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[1H-PYRAZOLO[3, 4-D]PYRIMIDIN-4-YL]-PIPERIDINE OR -PIPERAZINE COMPOUNDS AS SERINE-THEORONINE KINASE MODULATORS (P70S6K, ATK1 AND ATK2) FOR THE TREATMENT OF IMMUNOLOGICAL, INFLAMMATORY AND PROLIFERATIVE DISEASES

Abstract:

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(71) Applicant *(for all designated States except US)*: **EXELIXIS, INC.** [US/US]; 170 HARBOR WAY, P.o. Box 511, South San Francisco, California 94083-0511 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **RICE, Ken** [US/US]; 802 Autumn Lane, Mill Valley, California 94941 (US). **CO, Erick, Wang** [US/US]; 864 Boardwalk Place, Redwood City, California 94065 (US). **KIM, Moon, Hwan** [US/US]; 1128 Oregon Avenue, Palo Alto, California 94303 (US). **BANNEN, Lynn, Canne** [US/US]; 1086 Rio Vista Drive, Pacifica, California 94044 (US). **BUSSENIUS, Joerg** [DE/US]; 1042 Helm Lane, Foster City, California 94404 (US). **LE, Donna** [US/US]; 1855 Ribisi Way, San Jose, California 95131 (US). **TSUHAKO, Amy, Lew** [US/US]; 1232 Madruga Way, Milpitas, California 95035 (US). **NUSS, John** [US/US]; 16 Woodranch Circle, Danville, California 94526 (US). **WANG, Yong** [US/US]; 667 CATAMARAN STREET, Apt. #4, Foster City, California 94404 (US). **XU, Wei** [CN/US]; 327 Glasgow Circle, Danville, California 94526 (US). **KLEIN, Rhett, Ronald** [US/US]; 730 W. Schubert Avenue, Chicago, Illinois 60614 (US).

(74) Agent: **GREENFIELD, Michael, S.**; MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP, 300 SOUTH WACKER DRIVE, Suite 3100, Chicago, Illinois 60606 (US).

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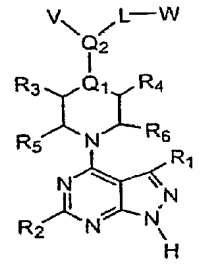

(I)

(57) Abstract: The invention provides compounds of formula (I) and methods for inhibition of kinases, more specifically p70S6 kinases, and more preferably p70S6, Akt-1 and Akt-2 kinases. The invention provides compounds for modulating protein kinase enzymatic activity for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration, chemoinvasion and metabolism. Compounds of the invention inhibit, regulate and/or modulate kinase receptor signal transduction pathways related to the changes in cellular activities as mentioned above, and the invention includes compositions which contain these compounds, and methods of using them to treat kinase-dependent diseases and conditions.

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[1H-PYRAZOLO[3,4-D]PYRIMIDIN-4-YL]-PIPERIDINE OR -PIPERAZINE COMPOUNDS AS SERINE-THEORONINE KINASE MODULATORS (P70S6K, ATK1 AND ATK2) FOR THE TREATMENT OF IMMUNOLOGICAL, INFLAMMATORY AND PROLIFERATIVE DISEASES

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] This invention relates to compounds for modulating protein kinase enzymatic activity for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration, chemoinvasion and metabolism. Even more specifically, the invention relates to compounds which inhibit, regulate and/or modulate kinase receptor signal transduction pathways related to the changes in cellular activities as mentioned above, compositions which contain these compounds, and methods of using them to treat kinase-dependent diseases and conditions.

Summary of Related Art

[0002] Improvements in the specificity of agents used to treat cancer is of considerable interest because of the therapeutic benefits which would be realized if the side effects associated with the administration of these agents could be reduced. Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms.

[0003] Protein kinases are enzymes that catalyze the phosphorylation of proteins at the hydroxy groups of tyrosine, serine and threonine residues of proteins. The kinase complement of the human genome contains 518 putative protein kinase genes [Manning et al, Science, (2002), 298, 1912]. The consequences of this activity include effects on cell differentiation, proliferation, transcription, translation, metabolism, cell cycle progression, apoptosis, metabolism cytoskeletal rearrangement and movement; i.e., protein kinases mediate the majority of signal transduction in eukaryotic cells. Furthermore, abnormal protein kinase activity has been related to a host of disorders, ranging from relatively non-life threatening diseases such as psoriasis to cancer. Chromosomal mapping has revealed that over 200 kinases map to disease loci, including cancer, inflammatory and metabolic disease.

[0004] Tyrosine kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases have an extracellular, a transmembrane, and an intracellular portion, while non-receptor type tyrosine kinases are wholly intracellular.

[0005] Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. In fact, about 20 different subfamilies of receptor-type tyrosine kinases have been identified. One tyrosine kinase subfamily, designated the HER subfamily, is comprised of EGFR (HER1), HER2, HER3, and HER4. Ligands of this subfamily of receptors identified so far include epithelial growth factor, TGF-alpha, amphiregulin, HB-EGF, betacellulin and heregulin. Another subfamily of these receptor-type tyrosine kinases is the insulin subfamily, which includes INS-R, IGF-IR, and IR-R. The PDGF subfamily includes the PDGF-alpha and -beta receptors, CSFIR, c-kit and FLK-II. Then there is the FLK family, which is comprised of the kinase insert domain receptor (KDR), fetal liver kinase-1 (FLK-1), fetal liver kinase-4 (FLK-4) and the fms-like tyrosine kinase-1 (Flt-1). The PDGF and FLK families are usually considered together due to the similarities of the two groups. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., DN&P 7(6): 334-339, 1994, which is hereby incorporated by reference.

[0006] The non-receptor type of tyrosine kinases is also comprised of numerous subfamilies, including Src, Frk, Btk, Csk, Abl, Syk/Zap70, Fes/Fps, Fak, Jak, and Ack. Each of these subfamilies is further sub-divided into varying receptors. For example, the Src subfamily is one of the largest and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr, and Yrk. The Src subfamily of enzymes has been linked to oncogenesis. For a more detailed discussion of the non-receptor type of tyrosine kinases, see Bolen, Oncogene, 8:2025-2031 (1993), which is hereby incorporated by reference.

[0007] Serine-theoronine kinases play critical roles in intracellular signal transduction and include the multiple families, including STE, CKI, AGC, CAMK, and CMGC. Important subfamilies include, the MAP kinases, p38, JNK and ERK, which modulate signal transduction resulting from such diverse stimuli as mitogenic, stress, proinflammatory and antiapoptotic pathways. Members of the MAP kinase subfamily have been targeted for therapeutic intervention, including p38a, JNK isozymes and Raf.

[0008] Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases. These include, but are not limited to: immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Therefore, both receptor and non-receptor protein kinases are attractive targets for small molecule drug discovery.

[0009] One particularly attractive goal for therapeutic use of kinase modulation relates to oncological indications. For example, modulation of protein kinase activity for the treatment of cancer has been demonstrated successfully with the FDA approval of Gleevec® (imatinib mesylate, produced by Novartis Pharmaceutical Corporation of East Hanover, NJ) for the treatment of Chronic Myeloid Leukemia (CML) and gastrointestinal stroma cancers. Gleevec is a selective Abl kinase inhibitor.

[0010] Modulation (particularly inhibition) of cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. Drug Disc Technol 2001 6, 1005-1024), is an attractive goal for development of small-molecule drugs. Anti-angiogenic therapy represents a potentially important approach for the treatment of solid tumors and other diseases associated with dysregulated vascularization, including ischemic coronary artery disease, diabetic retinopathy, psoriasis and rheumatoid arthritis. As well, cell antiproliferative agents are desirable to slow or stop the growth of tumors.

[0011] The enzyme p70S6 kinase (p70S6K) is a serine-theoronine kinase that is a component of the phosphatidylinositol 3 kinase (PI3K)/Akt kinase pathway. Both Akt and p70S6K are downstream of phosphatidylinositol-3 kinase (PI3K), and undergo phosphorylation and activation in response to growth factors such as IGF-1, EGF, TGF-α and HGF. The enzyme p70S6K modulates protein synthesis by phosphorylation of the S6 ribosomal protein promoting translation. A role for p70S6K in tumor cell proliferation and protection of cells from apoptosis is supported based on its participation in growth factor receptor signal transduction, overexpression and activation in tumor tissues [Pene et al (2002) Oncogene 21, 6587; Miyakawa et al (2003) Endocrin J. 50, 77, 83; Le et al (2003) Oncogene 22, 484]. Clinical inhibition of p70S6K activation was observed in renal carcinoma patients treated with

CCI-779 (rapamycin ester), an inhibitor of the upstream activating kinase, mTOR. A significant linear association between disease progression and inhibition of p70S6K activity was reported [Peralba et al (2003) Clinical Cancer Research 9, 2887].

[0012] Recently, the enzyme p70S6K was found to be implicated in metabolic diseases and disorders. It was reported that the absence of P70S6K protects against age- and diet-induced obesity while enhancing insulin sensitivity [Um et al (2004) Nature 431, 200-205 and Pende et al (2000) Nature 408, 994-997]. A role for p70S6K in metabolic diseases and disorders such as obesity, diabetes, metabolic syndrome, insulin resistance, hyperglycemia, hyperaminoacidemia, and hyperlipidemia is supported based upon the findings.

[0013] Phosphoinositide 3-kinases, or PI3Ks, generate specific inositol lipids implicated in the regulation of cell growth, proliferation, survival, differentiation, metabolism and cytoskeletal changes. One of the best-characterized targets of PI3K lipid products is the serine threonine protein kinase AKT, or protein kinase B (PKB). In quiescent cells, AKT resides in the cytosol in a low-activity conformation. Upon cellular stimulation, AKT is activated through recruitment to cellular membranes by PI3K lipid products and by phosphorylation by 3-prime phosphoinositide-dependent kinase-1 (PDPK1), leading to a cascade of downstream effects through activation of a range of downstream targets including glycogen synthase kinase-3beta (GSK-3beta), mammalian target of rapamycin (mTOR), p70S6 kinase, endothelial nitric oxide synthase (eNOS) and several anti-apoptotic effectors [Hajduch, Eet al (2001) FEBS Lett. 492: 199-203; Vanhaesebroeck, B. and Alessi, D. R. (2000) Biochem. J. 346: 561-576]. To date, three isoforms of AKT, namely AKT1, AKT2, and AKT3, have been identified.

[0014] AKT1 plays an important role in neuronal and general cellular survival, and resistance to apoptosis [Dudek H. et al (1997) Science 275: 661-663; Kauffmann-Zeh A, et al (1997) Nature 385: 544-548; Songyang Z. et al (1997) Proc Natl Acad Sci U S A 94: 11345-11350]. AKT1 has been implicated in a wide variety of cancers, including breast and thyroid cancer [Liang J. et al (2002) Nature Med. 8: 1153-1160; Vasco V et al (2004) J. Med. Genet. 41: 161-170]. AKT1 also play a role in metabolism through control of pancreatic beta-cell growth and survival [Dickson LM, and Rhodes CJ (2004) Am J Physiol Endocrinol Metab. 287:E192-8].

[0015] AKT2 is enriched in insulin-responsive tissues and has been implicated in the metabolic actions of the hormone, such as diabetes [George S et al (2004) Science 304: 1325-

1328]. AKT2 is amplified and overexpressed in ovarian cancer, and its overexpression contributes to the malignant phenotype of a subset of human ductal pancreatic cancers [Cheng, J. Q. et al (1992) Proc. Nat. Acad. Sci. 89: 9267-9271; Cheng, J. Q. et al (1996) Proc. Nat. Acad. Sci. 93: 3636-3641].

[0016] Accordingly, the identification of small-molecule compounds that specifically inhibit, regulate and/or modulate the signal transduction of kinases, particularly p70S6K, AKT1 and AKT2 is desirable as a means to treat or prevent disease states associated with abnormal cell proliferation and metabolism is an object of this invention.

SUMMARY OF THE INVENTION

[0017] In one aspect, the present invention provides compounds for modulating the activity of kinases, preferably p70S6, Akt-1 or Akt-2 kinases, and methods of treating diseases mediated by the activity of kinases, prefereably p70S6, Akt-1 or Akt-2 kinases utilizing the compounds and pharmaceutical compositions thereof. Diseases mediated by p70S6, Akt-1 and/or Akt-2 kinase activity include, but are not limited to, diseases characterized in part by migration, invasion, proliferation, and other biological activities associated with invasive cell growth, and metabolism.

[0018] In another aspect, the invention provides methods of screening for modulators of kinases activity, preferably p70S6, Akt-1 and/or Akt-2 activity. The methods comprise combining a composition of the invention, typically a kinase, preferably p70S6, Akt-1 and/or Akt-2 kinases, and at least one candidate agent and determining the effect of the candidate agent on the kinases activity.

[0019] In yet another aspect, the invention also provides pharmaceutical kits comprising one or more containers filled with one or more of the ingredients of pharmaceutical compounds and/or compositions of the present invention, including, kinase enzyme activity modulators, preferably p70S6, Akt-1 and/or Akt-2 kinase enzyme activity modulators as described herein. Such kits can also include, for example, other compounds and/or compositions (e.g., diluents, permeation enhancers, lubricants, and the like), a device(s) for administering the compounds and/or compositions, and written instructions in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which

instructions can also reflects approval by the agency of manufacture, use or sale for human administration.

[0020] In still yet another aspect, the invention also provides a diagnostic agent comprising a compound of the invention and, optionally, pharmaceutically acceptable adjuvants and excipients.

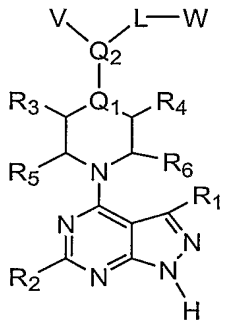
[0021] These and other features and advantages of the present invention will be described in more detail below with reference to the associated drawings.

DETAILED DESCRIPTION OF THE INVENTION

[0022] The compositions of the invention are used to treat diseases associated with abnormal and or unregulated cellular activities. Disease states which can be treated by the methods and compositions provided herein include, but are not limited to, cancer (further discussed below), immunological disorders such as rheumatoid arthritis, graft-host diseases, multiple sclerosis, psoriasis; cardiovascular diseases such as artheroscrosis, myocardioinfarction, ischemia, stroke and restenosis; metabolic disorders and diseases such as diabetes, obesity and hypercholesterolemia; and other inflammatory and degenerative diseases such as interbowel diseases, osteoarthritus, macular degeneration, diabetic retinopathy.

[0023] It is appreciated that in some cases the cells may not be in a hyper- or hypo-proliferative and/or migratory state (abnormal state) and still require treatment. For example, during wound healing, the cells may be proliferating "normally", but proliferation and migration enhancement may be desired. Alternatively, reduction in "normal" cell proliferation and/or migration rate may be desired.

[0024] The present invention comprises a compound for modulating kinase activity, preferably p70S6, Akt-1 and/or Akt-2 kinase activity according to Formula **I**,



and pharmaceutically acceptable salts, hydrates and prodrugs thereof wherein:

R_1 is H, halo, cyano, aryl, heteroaryl, C_{1-4} alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein the aryl, heteroaryl, alkyl, alkenyl and alkynyl are optionally substituted with one or two groups independently selected from CO_2R_{10}, $CONR_{10}R_{11}$, OR_{10}, and $NR_{10}R_{11}$;

R_2 is H, NH_2, SH, OH, or C_1-C_2 alkyl;

R_3, R_4, R_5, and R_6 are each independently H, oxo, CO_2R_{10}, $CONR_{10}R_{11}$, C_{1-4} alkyl, C_1-C_6 alkoxy, or C_1-C_6 alkoxy-C_1-C_4 alkyl, wherein the C_1-C_4 alkyl, C_1-C_6 alkoxy and C_1-C_6 alkoxy-C_1-C_4 alkyl in each group are independently optionally substituted with 1 or 2 substituents independently selected from CO_2R_{10}, $CONR_{10}R_{11}$, OR_{10}, and $NR_{10}R_{11}$, or

R_3 and R_5 together with the carbons to which they are attached form a C_3-C_7 carbocyclic ring, wherein the ring is optionally substituted with H, halo, cyano, nitro, or amino,

R_4 and R_6 together with the carbons to which they are attached form a C_3-C_7 carbocyclic ring, wherein the ring is optionally substituted with H, halo, cyano, nitro, or amino,

R_3 and R_6 together with the carbons to which they are attached form a bridged C_5-C_7 carbocyclic ring, wherein the ring is optionally substituted with H, halo, cyano, nitro, or amino, or

R_4 and R_5 together with the carbons to which they are attached form a bridged C_5-C_7 carbocyclic ring, wherein the ring is optionally substituted with H, halo, cyano, nitro, or amino;

L is C_{0-4} alkyl, C_2-C_6 alkenyl, $-N(R_{12})-$, $-C(O)N(R_{12})-$, $-N(R_{12})C(O)-$, $-C(O)-$, $-O-(CH_2)_n-$, or $-(CH_2)_n-O-$, wherein n is 1-4;

Q_1 is N or CR_{13}, wherein R_{13} is H or $C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$;

Q_2 is a bond, CR_{14}, O, or N, wherein R_{14} is H, OH, C_{1-4} alkyl, C_{1-4} alkoxy, $NR_{15}R_{15}$, wherein R_{15} is H or C_{1-4} alkyl, or Q_2 and V together form C(=O);

when Q_2 is a bond,

V is absent and R_{13} is not H;

when Q_1 is CR_{13} and Q_2 is CH,

V is H, OH, NH_2, C_1-C_6 alkoxy, $NR_{10}R_{11}$, $O(CH_2)_nNR_{10}R_{11}$, $O(CH_2)_n$ attached to a C or N of a 4-7 membered heterocyclyl, $NR_{12}(CH_2)_nNR_{10}R_{11}$, $NR_{12}C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$, $NR_{12}C(O)(CH_2)_nNR_{10}R_{11}$, $(CH_2)_mO(CH_2)_nNR_{10}R_{11}$, $(CH_2)_mNR_{12}(CH_2)_nNR_{10}R_{11}$, $(CH_2)_mCHR_{12}(CH_2)_nNR_{10}R_{11}$, C_{1-4} alkyl optionally substituted with OH or $NR_{10}R_{11}$, or

V is a 4-7 membered unsaturated cyclic containing 1-3 atom of O or N, or

V is a bicyclic solublizing group;

when Q_1 is N and Q_2 is CH, or when Q_1 is CR_{13} and Q_2 is O or N,

V is H; $(CH_2)_mO(CH_2)_nNR_{10}R_{11}$, $(CH_2)_mNR_{12}(CH_2)_nNR_{10}R_{11}$, $(CH_2)_mCHR_{12}(CH_2)_nNR_{10}R_{11}$, $C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$, $C(O)(CH_2)_nNR_{10}R_{11}$, $C(O)O(CH_2)_nNR_{10}R_{11}$, $C(O)C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$, $SO_2(CH_2)_nNR_{10}R_{11}$, $C(O)$-C_2-C_6 alkenyl, or C_{1-4} alkyl optionally substituted with OH or $NR_{10}R_{11}$, or

V is a 4-7 membered saturated or unsaturated cyclic or heterocyclic containing 1-3 atoms of O or N, optionally substituted with 1 or 2 C_1-C_3 alkoxy groups or

V is a "bicyclic solublizing group";

m is 1-3,

n is 1-4

W is C_1-C_6 alkyl, $NR_{10}R_{11}$, or W is

aryl, C_3-C_7 cycloalkyl, heterocyclyl, heteroaryl, or 5-12 membered fused bicylic or tricyclic saturated, partially saturated, or usaturated ring system containing 0-4 ring atoms selected from N, O, and S, wherein each aryl, cycloalkyl, heterocyclyl, heteroaryl, and fused bicyclic or tricyclic ring system is optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2, CF_3, OH, $NR_{10}R_{11}$, C_1-C_6 alkoxy, C_1-C_6 alkyl, NO_2, $C(O)OC_1$-C_6 alkyl,

$C(O)NR_{12}$-C_1-C_6 alkoxy, $C(O)NR_{12}$-heterocyclyl, aryl, O-aryl, O-CH_2-aryl, N-aryl, wherein each aryl substituent is optionally further substituted with halo, or

V, Q_2, L, and W together form an aryl ring, heteroaryl ring, C_3-C_7 cycloalkyl ring, heterocyclyl ring, or a 5-12 membered fused bicylic or tricyclic saturated, partially saturated or usaturated ring system containing 0-4 ring atoms selected from N, O, and S, wherein each ring or ring system is optionally substituted with 1, 2, or 3 groups independently selected from halo, CN, NO_2, CF_3, OH, $NR_{10}R_{11}$, C_1-C_6 alkoxy, C_1-C_6 alkyl, NO_2, $C(O)OC_1$-C_6 alkyl, $C(O)NR_{12}$-C_1-C_6 alkoxy, $C(O)NR_{12}$-heterocyclyl, aryl, aryl, O-aryl, NH-aryl, wherein each aryl substituent is optionally further substituted with halo; and

R_{10}, R_{11} and R_{12} are each independently H or C_1-$_6$ alkyl which is optionally substituted with aryl or heteroaryl.

[0025] In a preferred embodiment, the following compounds are excluded as compounds of Formula I:

4-(4-(2-fluorophenyl)piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine;
4-(4-(3-chlorophenyl)piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine;
ethyl 4-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate;
tert-butyl 4-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate; and
N-(4-phenoxyphenyl)-4-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazine-1-carboxamide.

[0026] Preferred compounds of Formula I include compounds of Formula II, which are compounds of Formula I wherein R_1 is not hydrogen.

[0027] Preferred compounds of Formula II include compounds wherein R_1 is halo, C_1-C_4 alkyl, OH, cyano, or amino.

[0028] Preferred compounds of Formula II include compounds wherein R_1 is halo.

[0029] Preferred compounds of Formula II incude compounds wherein R_1 is bromo.

[0030] Preferred compounds of Formula II include compounds wherein R_2 is H.

[0031] Preferred compounds of Formula II include compounds wherein R_3, R_4, R_5, and R_6, are each H.

[0032] Preferred compounds of Formula I and II include compounds of Formula III, which are compounds of Formula I or Formula II wherein Q_1 is CH and Q_2 is CH.

[0033] Preferred compounds of Formula III include compounds wherein L is a bond.

[0034] Preferred compounds of Formula III include compounds wherein W is aryl optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2, CF_3, OH, $NR_{10}R_{11}$, C_1-C_6 alkoxy, C_1-C_6 alkyl, NO_2, $C(O)OC_1$-C_6 alkyl, $C(O)NR_{12}$-C_1-C_6 alkoxy, $C(O)NR_{12}$-heterocyclyl, aryl, O-aryl, O-CH_2-aryl, NH-aryl, wherein each aryl substituent is optionally further substituted with halo.

[0035] Preferred compounds of Formula III include compounds wherein W is phenyl optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2, CF_3, OH, $NR_{10}R_{11}$, C_1-C_6 alkoxy, C_1-C_6 alkyl, NO_2, $C(O)OC_1$-C_6 alkyl, $C(O)NR_{12}$-C_1-C_6 alkoxy, $C(O)NR_{12}$-heterocyclyl, aryl, O-aryl, O-CH_2-aryl, N-aryl, wherein each aryl substituent is optionally further substituted with halo.

[0036] Preferred compounds of Formula III include compounds wherein W is phenyl optionally substituted with 1, or 2 substituents independently selected from halo, CF_3, C_1-$_4$ alkyl, and C_1-C_4 alkoxy.

[0037] Preferred compounds of Formula III include compounds wherein W is phenyl optionally substituted with 1, or 2 substituents independently selected from F, Cl and Br.

[0038] Preferred compounds of Formula III include compounds wherein V is H, OH, $O(CH_2)_nNR_{10}R_{11}$, $NR_{12}(CH_2)_nNR_{10}R_{11}$, $NR_{12}C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$, or $NR_{12}C(O)(CH_2)_nNR_{10}R_{11}$.

[0039] Preferred compounds of Formula III include compounds wherein V is H, OH, $O(CH_2)_nNR_{10}R_{11}$, $NR_{12}(CH_2)_nNR_{10}R_{11}$, $NR_{12}C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$, or $NR_{12}C(O)(CH_2)_nNR_{10}R_{11}$ and R_{10} and R_{11} are each CH_3.

[0040] Preferred compounds of Formula III include compounds wherein R_1 is H, halo or C_1-C_2 alkyl and R_2 is H.

[0041] Preferred compounds of Formula III include compounds wherein R_3, R_4, R_5, and R_6, are each H.

[0042] Preferred compounds of Formula I and II include compounds of Formula IV, which are compounds of Formula I or Formula II wherein Q_1 is N and Q_2 is CH.

[0043] Preferred compounds of Formula IV include compounds wherein L is a bond.

[0044] Preferred compounds of Formula IV include compounds wherein W is aryl optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2, CF_3, OH, $NR_{10}R_{11}$, C_1-C_6 alkoxy, C_1-C_6 alkyl, NO_2, $C(O)OC_1$-C_6 alkyl, $C(O)NR_{12}$-C_1-C_6 alkoxy,

$C(O)NR_{12}$-heterocyclyl, aryl, O-aryl, O-CH_2-aryl, N-aryl, wherein each aryl substituent is optionally further substituted with halo.

[0045] Preferred compounds of Formula IV include compounds wherein W is phenyl optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2, CF_3, OH, $NR_{10}R_{11}$, C_1-C_6 alkoxy, C_1-C_6 alkyl, NO_2, $C(O)OC_1$-C_6 alkyl, $C(O)NR_{12}$-C_1-C_6 alkoxy, $C(O)NR_{12}$-heterocyclyl, aryl, O-aryl, O-CH_2-aryl, N-aryl, wherein each aryl substituent is optionally further substituted with halo.

[0046] Preferred compounds of Formula IV include compounds wherein W is phenyl optionally substituted with 1, or 2 substituents independently selected from halo, CF_3, C_1-$_4$ alkyl, and C_1-C_4 alkoxy.

[0047] Preferred compounds of Formula IV include compounds wherein W is phenyl optionally substituted with 1, or 2 substituents independently selected from F, Cl and Br.

[0048] Preferred compounds of Formula IV include compounds wherein V is H, $C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$, or C_{1-4} alkyl.

[0049] Preferred compounds of Formula IV include compounds wherein V is H, $C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$, or C_{1-4} alkyl and R_{10} and R_{11} are each CH_3.

[0050] Preferred compounds of Formula IV include compounds wherein V is H.

[0051] Preferred compounds of Formula IV include compounds wherein R_1 is halo and R_2 is H.

[0052] Preferred compounds of Formula IV include compounds wherein R_3, R_4, R_5, and R_6, are each H.

[0053] Preferred compounds of Formula I and II include compounds of Formula V, which are compounds of Formula I or Formula II wherein Q_1 is CH and Q_2 is N.

[0054] Preferred compounds of Formula V include compounds wherein L is a bond.

[0055] Preferred compounds of Formula V include compounds wherein W is aryl optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2, CF_3, OH, $NR_{10}R_{11}$, C_1-C_6 alkoxy, C_1-C_6 alkyl, NO_2, $C(O)OC_1$-C_6 alkyl, $C(O)NR_{12}$-C_1-C_6 alkoxy, $C(O)NR_{12}$-heterocyclyl, aryl, O-aryl, O-CH_2-aryl, N-aryl, wherein each aryl substituent is optionally further substituted with halo.

[0056] Preferred compounds of Formula V include compounds wherein W is phenyl optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2, CF_3, OH,

$NR_{10}R_{11}$, C_1-C_6 alkoxy, C_1-C_6 alkyl, NO_2, $C(O)OC_1$-C_6 alkyl, $C(O)NR_{12}$-C_1-C_6 alkoxy, $C(O)NR_{12}$-heterocyclyl, aryl, O-aryl, O-CH_2-aryl, N-aryl, wherein each aryl substituent is optionally further substituted with halo.

[0057] Preferred compounds of Formula V include compounds wherein W is phenyl optionally substituted with 1, or 2 substituents independently selected from halo, CF_3, C_1-$_4$ alkyl, and C_1-C_4 alkoxy.

[0058] Preferred compounds of Formula V include compounds wherein W is phenyl optionally substituted with 1, or 2 substituents independently selected from F, Cl and Br.

[0059] Preferred compounds of Formula V include compounds wherein V is H, $C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$, C(O) $(CH_2)_nNR_{10}R_{11}$, $C(O)O(CH_2)_nNR_{10}R_{11}$, $C(O)C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$, $SO_2(CH_2)_nNR_{10}R_{11}$, C(O)-$C_2$-$C_6$ alkenyl, or C_1-$_4$ alkyl optionally substituted with $NR_{10}R_{11}$.

[0060] Preferred compounds of Formula V include compounds wherein V is H, $C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$, C(O) $(CH_2)_nNR_{10}R_{11}$, $C(O)O(CH_2)_nNR_{10}R_{11}$, $C(O)C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$, $SO_2(CH_2)_nNR_{10}R_{11}$, C(O)-$C_2$-$C_6$ alkenyl, or C_1-$_4$ alkyl optionally substituted with $NR_{10}R_{11}$ and R_{10} and R_{11} are each CH_3.

[0061] Preferred compounds of Formula V include compounds wherein R_1 is halo and R_2 is H.

[0062] Preferred compounds of Formula V include compounds wherein R_3, R_4, R_5, and R_6, are each H.

[0063] Preferred compounds of Formula I and II include compounds of Formula VI, which are compounds of Formula I or Formula II wherein Q_1 is CH or N, and Q_2 and V together form C(=O).

[0064] Preferred compounds of Formula VI include compounds wherein L is a bond.

[0065] Preferred compounds of Formula VI include compounds wherein W is aryl optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2, CF_3, OH, $NR_{10}R_{11}$, C_1-C_6 alkoxy, C_1-C_6 alkyl, NO_2, $C(O)OC_1$-C_6 alkyl, $C(O)NR_{12}$-C_1-C_6 alkoxy, $C(O)NR_{12}$-heterocyclyl, aryl, O-aryl, O-CH_2-aryl, N-aryl, wherein each aryl substituent is optionally further substituted with halo.

[0066] Preferred compounds of Formula VI include compounds wherein W is phenyl optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2, CF_3, OH, $NR_{10}R_{11}$, C_1-C_6 alkoxy, C_1-C_6 alkyl, NO_2, $C(O)OC_1$-C_6 alkyl, $C(O)NR_{12}$-C_1-C_6

alkoxy, $C(O)NR_{12}$-heterocyclyl, aryl, O-aryl, O-CH_2-aryl, N-aryl, wherein each aryl substituent is optionally further substituted with halo.

[0067] Preferred compounds of Formula VI include compounds wherein W is phenyl optionally substituted with 1, or 2 substituents independently selected from halo, CF_3, C_{1-4} alkyl, and C_1-C_4 alkoxy.

[0068] Preferred compounds of Formula VI include compounds wherein W is phenyl optionally substituted with 1, or 2 substituents independently selected from F, Cl and Br.

[0069] Preferred compounds of Formula VI include compounds wherein R_1 is halo and R_2 is H.

[0070] Preferred compounds of Formula VI include compounds wherein R_3, R_4, R_5, and R_6, are each H.

[0071] In another example, the compound is according to paragraph [0024], selected from

Table 1

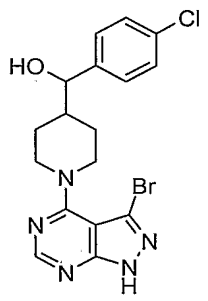
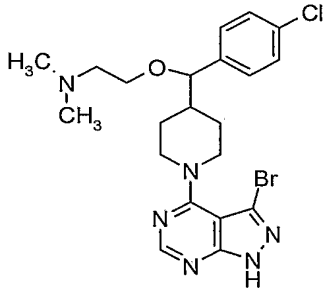
Entry	Name	Structure
1	[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methanol	
2	2-{[[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]oxy}-N,N-dimethylethanamine	

Table 1

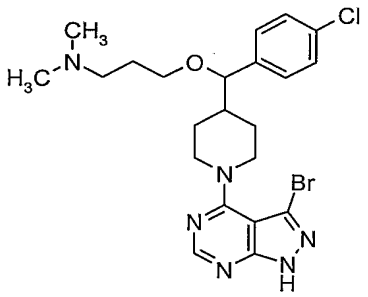
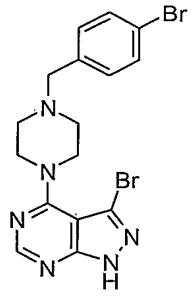
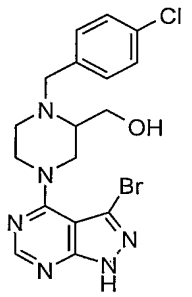
Entry	Name	Structure
3	3-{[[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]oxy}-N,N-dimethylpropan-1-amine	
4	3-bromo-4-{4-[(4-bromophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	
5	{4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-1-[(4-chlorophenyl)methyl]piperazin-2-yl}methanol	

Table 1

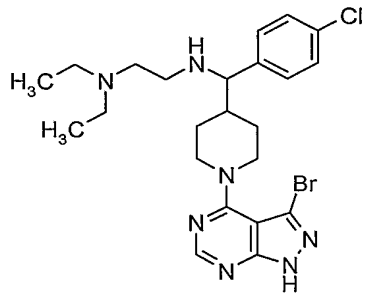
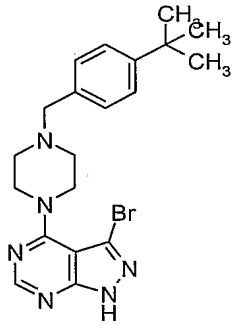
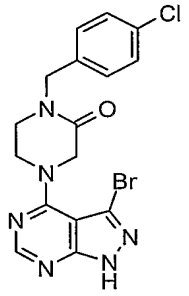
Entry	Name	Structure
6	N'-[[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]-N,N-diethylethane-1,2-diamine	
7	3-bromo-4-(4-{[4-(1,1-dimethylethyl)phenyl]methyl}piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine	
8	4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-1-[(4-chlorophenyl)methyl]piperazin-2-one	

Table 1

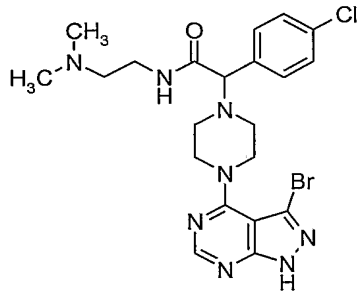
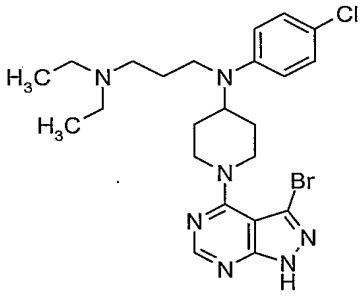
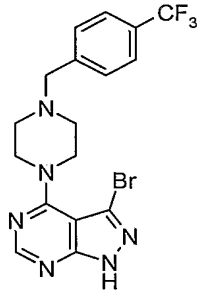
Entry	Name	Structure
9	2-[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-(4-chlorophenyl)-N-[2-(dimethylamino)ethyl]acetamide	
10	N-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-N-(4-chlorophenyl)-N',N'-diethylpropane-1,3-diamine	
11	3-bromo-4-(4-{[4-(trifluoromethyl)phenyl]methyl}piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine	

Table 1

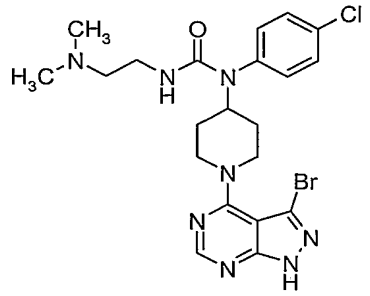
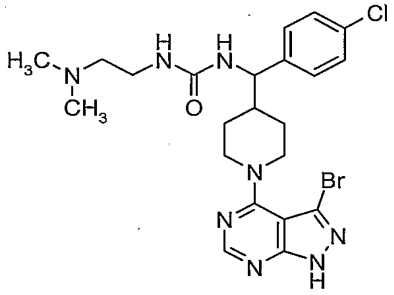
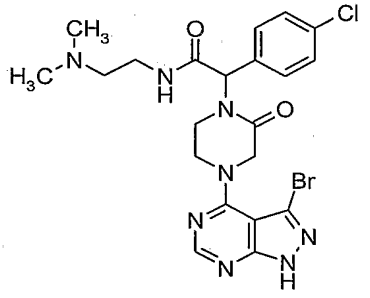
Entry	Name	Structure
12	N-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-N-(4-chlorophenyl)-N'-[2-(dimethylamino)ethyl]urea	
13	N-[[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]-N'-[2-(dimethylamino)ethyl]urea	
14	2-[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-2-oxopiperazin-1-yl]-2-(4-chlorophenyl)-N-[2-(dimethylamino)ethyl]acetamide	

Table 1

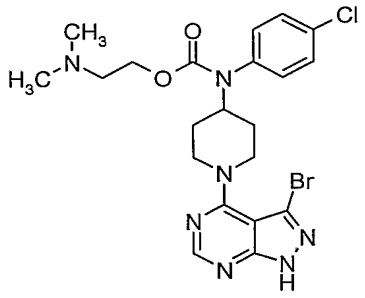
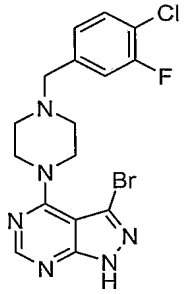
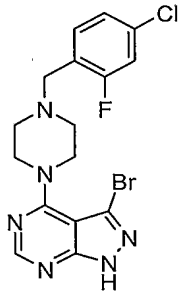
Entry	Name	Structure
15	2-(dimethylamino)ethyl [1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)carbamate	
16	3-bromo-4-{4-[(4-chloro-3-fluorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	
17	3-bromo-4-{4-[(4-chloro-2-fluorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	

Table 1

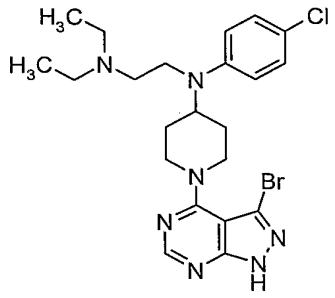
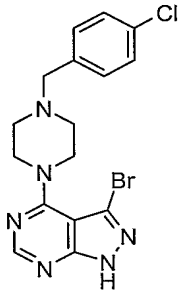
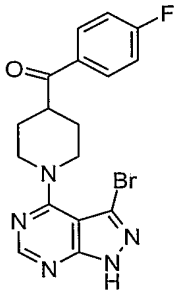
Entry	Name	Structure
18	N-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-N-(4-chlorophenyl)-N',N'-diethylethane-1,2-diamine	
19	3-bromo-4-{4-[(4-chlorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	
20	[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-fluorophenyl)methanone	

Table 1

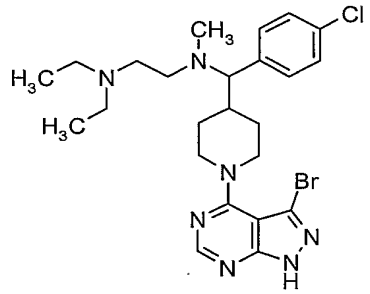
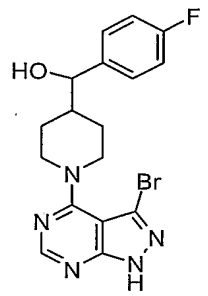
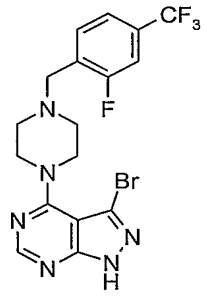
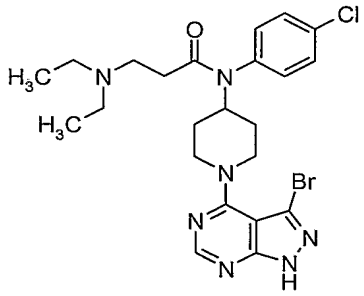
Entry	Name	Structure
21	N-[[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]-N',N'-diethyl-N-methylethane-1,2-diamine	
22	[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-fluorophenyl)methanol	
23	3-bromo-4-(4-{[2-fluoro-4-(trifluoromethyl)phenyl]methyl}piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine	
24	N-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-N-(4-chlorophenyl)-N~3~,N~3~-diethyl-beta-alaninamide	

Table 1

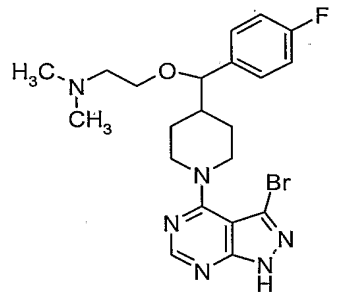
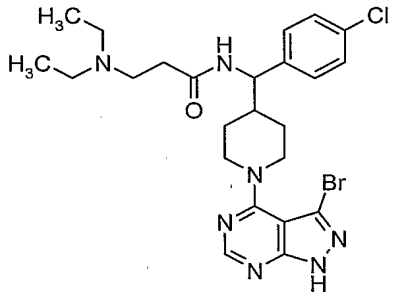
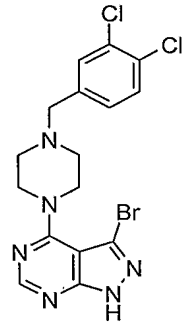
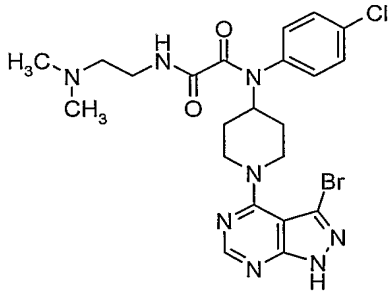
Entry	Name	Structure
25	2-{[[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-fluorophenyl)methyl]oxy}-N,N-dimethylethanamine	
26	N-[[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]-N~3~,N~3~-diethyl-beta-alaninamide	
27	3-bromo-4-{4-[(3,4-dichlorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	
28	N-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-N-(4-chlorophenyl)-N'-[2-(dimethylamino)ethyl]ethanediamide	

Table 1

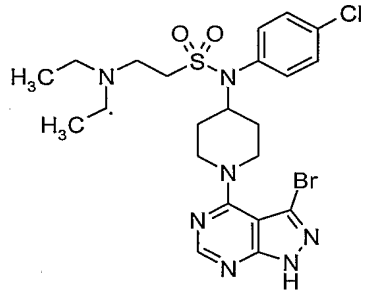
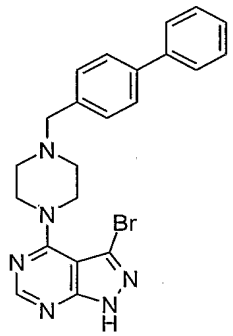
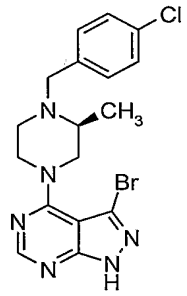
Entry	Name	Structure
29	N-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-N-(4-chlorophenyl)-2-(diethylamino)ethanesulfonamide	
30	4-[4-(biphenyl-4-ylmethyl)piperazin-1-yl]-3-bromo-1H-pyrazolo[3,4-d]pyrimidine	
31	3-bromo-4-{(3S)-4-[(4-chlorophenyl)methyl]-3-methylpiperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	

Table 1

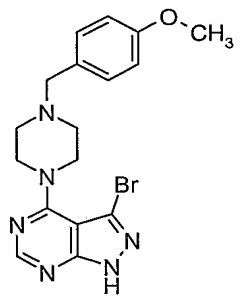
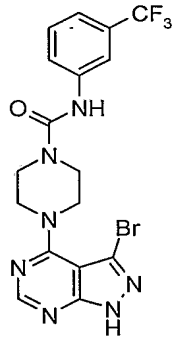
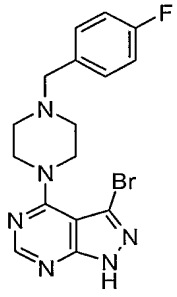
Entry	Name	Structure
32	3-bromo-4-(4-{[4-(methyloxy)phenyl]methyl}piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine	
33	4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-N-[3-(trifluoromethyl)phenyl]piperazine-1-carboxamide	
34	3-bromo-4-{4-[(4-fluorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	

Table 1

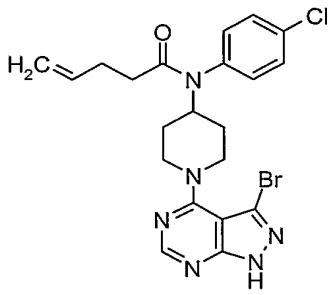
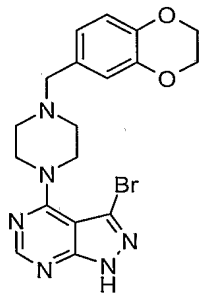
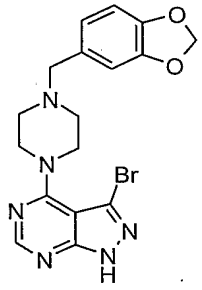
Entry	Name	Structure
35	N-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-N-(4-chlorophenyl)pent-4-enamide	
36	3-bromo-4-[4-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	
37	4-[4-(1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]-3-bromo-1H-pyrazolo[3,4-d]pyrimidine	

Table 1

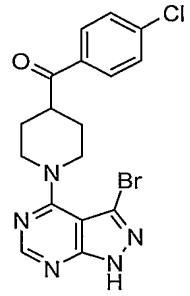
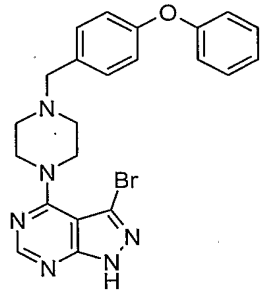
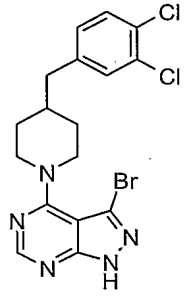
Entry	Name	Structure
38	[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methanone	
39	3-bromo-4-(4-{[4-(phenyloxy)phenyl]methyl}piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine	
40	3-bromo-4-{4-[(3,4-dichlorophenyl)methyl]piperidin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	

Table 1

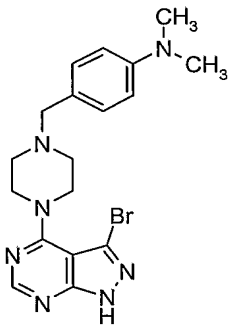
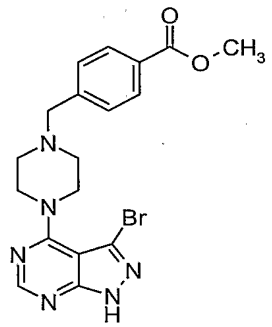
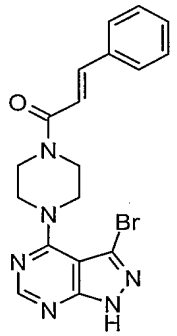
Entry	Name	Structure
41	4-{[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]methyl}-N,N-dimethylaniline	
42	methyl 4-{[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]methyl}benzoate	
43	3-bromo-4-{4-[(2E)-3-phenylprop-2-enoyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	

Table 1

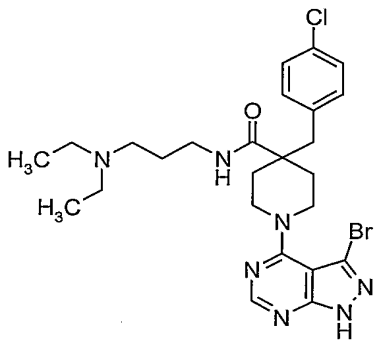
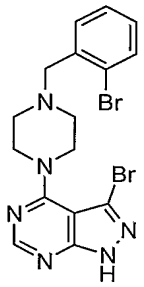
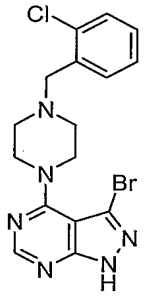
Entry	Name	Structure
44	1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-4-[(4-chlorophenyl)methyl]-N-[3-(diethylamino)propyl]piperidine-4-carboxamide	
45	3-bromo-4-{4-[(2-bromophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	
46	3-bromo-4-{4-[(2-chlorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	

Table 1

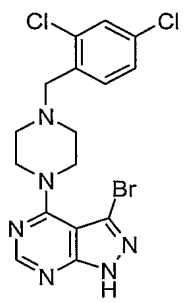
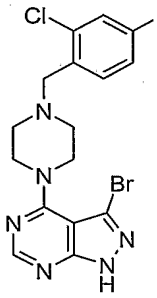
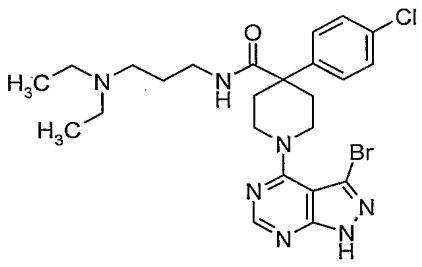
Entry	Name	Structure
47	3-bromo-4-{4-[(2,4-dichlorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	
48	3-bromo-4-{4-[(2-chloro-4-fluorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	
49	1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-4-(4-chlorophenyl)-N-[3-(diethylamino)propyl]piperidine-4-carboxamide	

Table 1

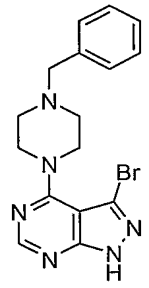
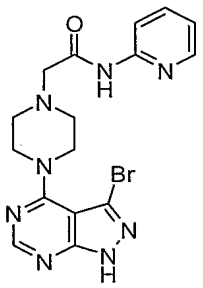
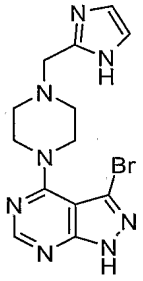
Entry	Name	Structure
50	3-bromo-4-[4-(phenylmethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	
51	2-[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-pyridin-2-ylacetamide	
52	3-bromo-4-[4-(1H-imidazol-2-ylmethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	

Table 1

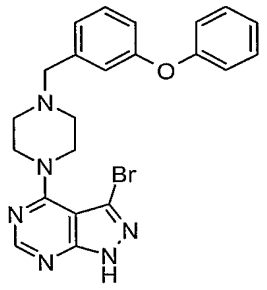
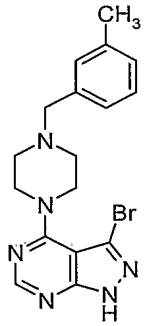
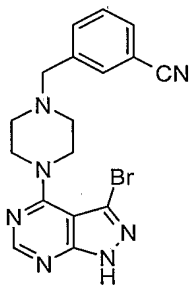
Entry	Name	Structure
53	3-bromo-4-(4-{[3-(phenyloxy)phenyl]methyl}piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine	
54	3-bromo-4-{4-[(3-methylphenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	
55	3-{[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]methyl}benzonitrile	

Table 1

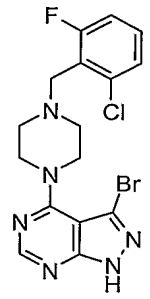
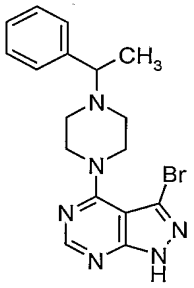
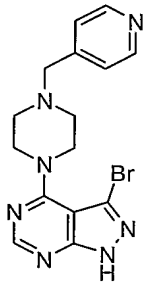
Entry	Name	Structure
56	3-bromo-4-{4-[(2-chloro-6-fluorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	
57	3-bromo-4-[4-(1-phenylethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	
58	3-bromo-4-[4-(pyridin-4-ylmethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	

Table 1

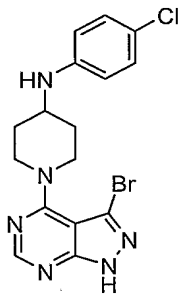
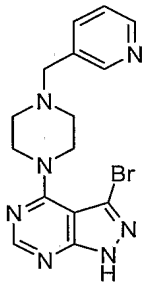
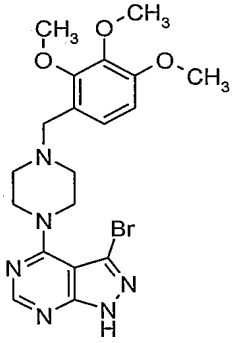
Entry	Name	Structure
59	1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-N-(4-chlorophenyl)piperidin-4-amine	
60	3-bromo-4-[4-(pyridin-3-ylmethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	
61	3-bromo-4-(4-{[2,3,4-tris(methyloxy)phenyl]methyl}piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine	

Table 1

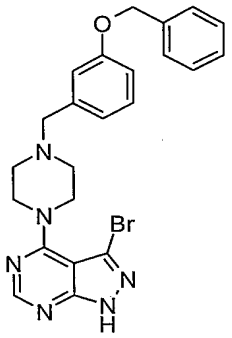
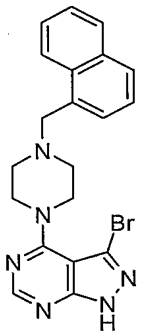
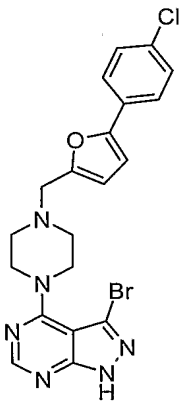
Entry	Name	Structure
62	3-bromo-4-[4-({3-[(phenylmethyl)oxy]phenyl}methyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	
63	3-bromo-4-[4-(naphthalen-1-ylmethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	
64	3-bromo-4-(4-{[5-(4-chlorophenyl)furan-2-yl]methyl}piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine	

Table 1

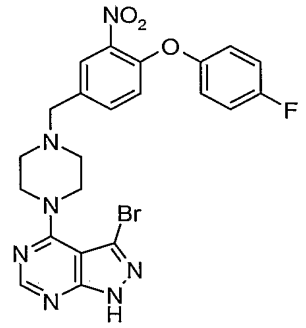
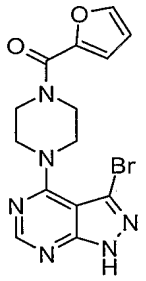
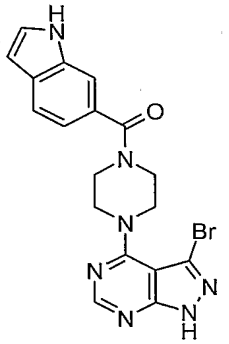
Entry	Name	Structure
65	3-bromo-4-[4-({4-[(4-fluorophenyl)oxy]-3-nitrophenyl}methyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	
66	3-bromo-4-[4-(furan-2-ylcarbonyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	
67	3-bromo-4-[4-(1H-indol-6-ylcarbonyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	

Table 1

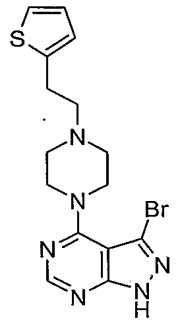
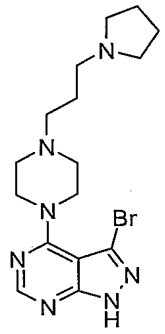
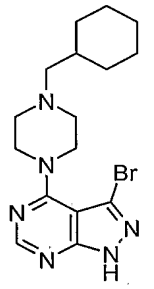
Entry	Name	Structure
68	3-bromo-4-{4-[2-(2-thienyl)ethyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	
69	3-bromo-4-[4-(3-pyrrolidin-1-ylpropyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	
70	3-bromo-4-[4-(cyclohexylmethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	

Table 1

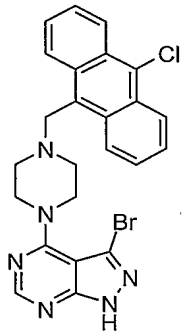
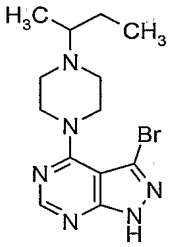
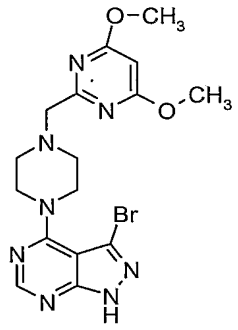
Entry	Name	Structure
71	3-bromo-4-{4-[(10-chloroanthracen-9-yl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	
72	3-bromo-4-[4-(1-methylpropyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	
73	4-(4-{[4,6-bis(methyloxy)pyrimidin-2-yl]methyl}piperazin-1-yl)-3-bromo-1H-pyrazolo[3,4-d]pyrimidine	

Table 1

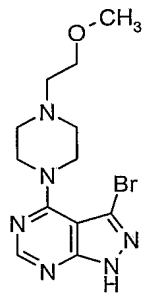
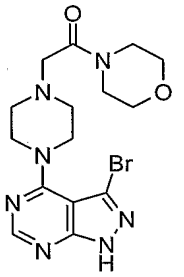
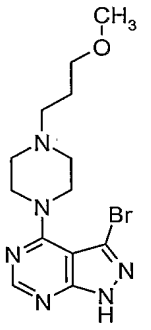
Entry	Name	Structure
74	3-bromo-4-{4-[2-(methyloxy)ethyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	
75	3-bromo-4-[4-(2-morpholin-4-yl-2-oxoethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	
76	3-bromo-4-{4-[3-(methyloxy)propyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	

Table 1

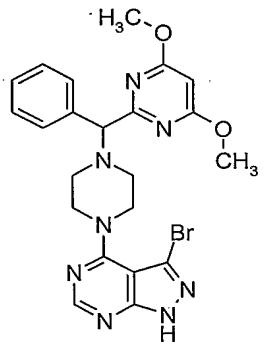
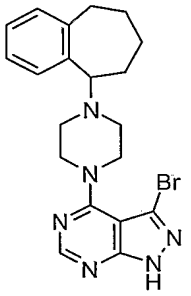
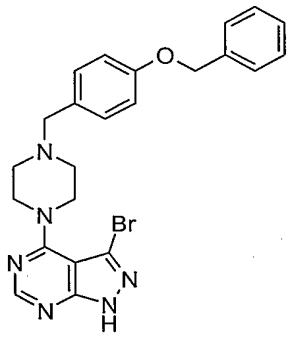
Entry	Name	Structure
77	4-{4-[[4,6-bis(methyloxy)pyrimidin-2-yl](phenyl)methyl]piperazin-1-yl}-3-bromo-1H-pyrazolo[3,4-d]pyrimidine	
78	3-bromo-4-[4-(6,7,8,9-tetrahydro-5H-benzocyclohepten-5-yl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	
79	3-bromo-4-[4-({4-[(phenylmethyl)oxy]phenyl}methyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	

Table 1

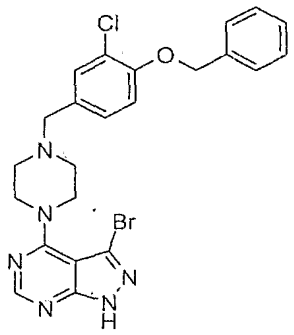
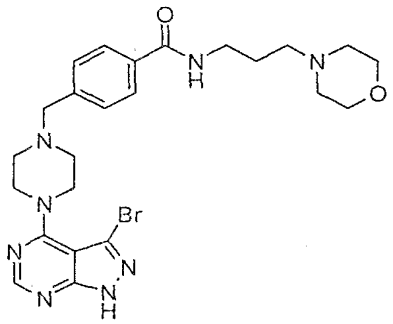
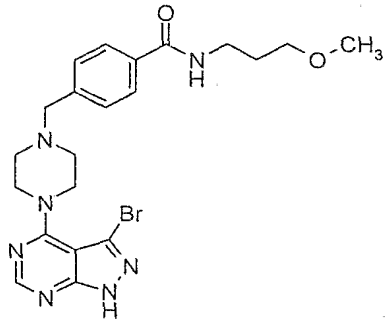
Entry	Name	Structure
80	3-bromo-4-[4-({3-chloro-4-[(phenylmethyl)oxy]phenyl}methyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	
81	4-{[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]methyl}-N-(3-morpholin-4-ylpropyl)benzamide	
82	4-{[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]methyl}-N-[3-(methyloxy)propyl]benzamide	

Table 1

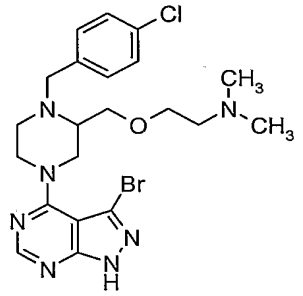
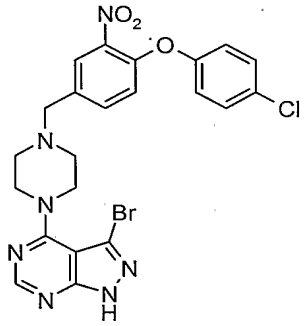
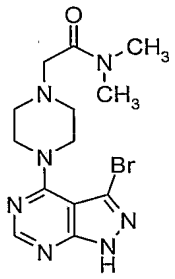
Entry	Name	Structure
83	2-[({4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-1-[(4-chlorophenyl)methyl]piperazin-2-yl}methyl)oxy]-N,N-dimethylethanamine	
84	3-bromo-4-[4-({4-[(4-chlorophenyl)oxy]-3-nitrophenyl}methyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	
85	2-[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N,N-dimethylacetamide	

Table 1

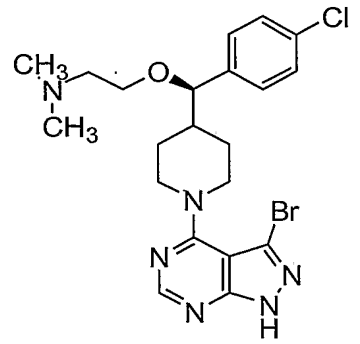
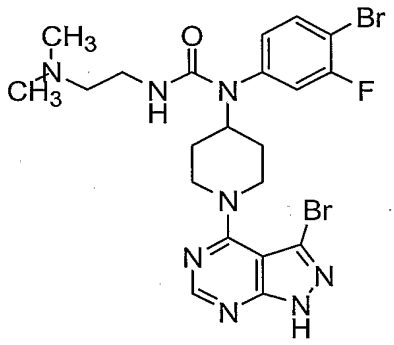
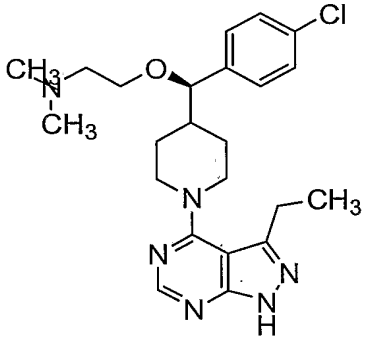
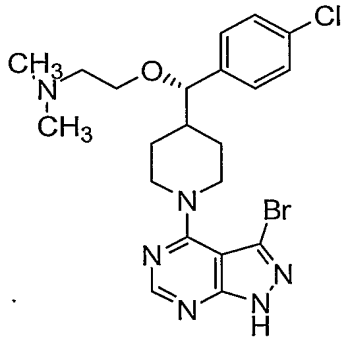
Entry	Name	Structure
86	2-{[(R)-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]oxy}-N,N-dimethylethanamine	
87	N-(4-bromo-3-fluorophenyl)-N-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-N'-[2-(dimethylamino)ethyl]urea	
88	2-({(R)-(4-chlorophenyl)[1-(3-ethyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]methyl}oxy)-N,N-dimethylethanamine	
89	2-{[(S)-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]oxy}-N,N-dimethylethanamine	

Table 1

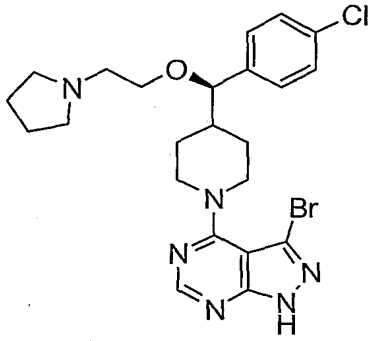
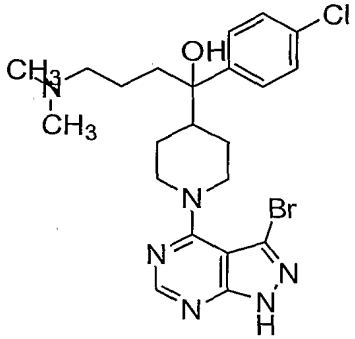
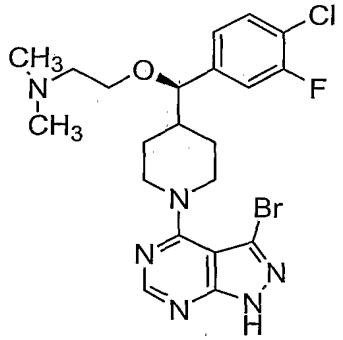
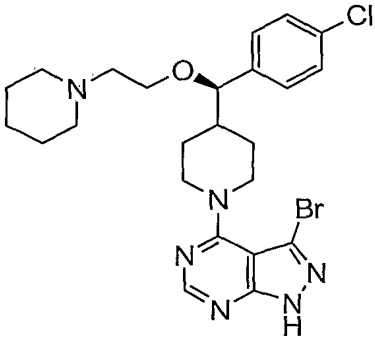
Entry	Name	Structure
90	3-bromo-4-(4-{(R)-(4-chlorophenyl)[(2-pyrrolidin-1-ylethyl)oxy]methyl}piperidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine	
91	1-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-1-(4-chlorophenyl)-4-(dimethylamino)butan-1-ol	
92	2-{[(R)-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chloro-3-fluorophenyl)methyl]oxy}-N,N-dimethylethanamine	
93	3-bromo-4-(4-{(R)-(4-chlorophenyl)[(2-piperidin-1-ylethyl)oxy]methyl}piperidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine	

Table 1

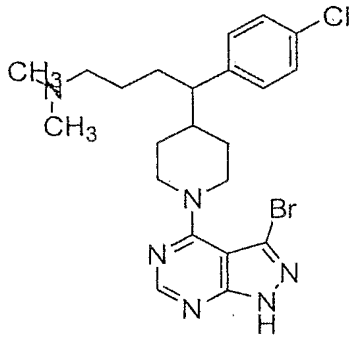
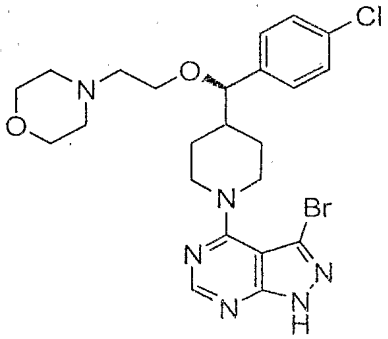
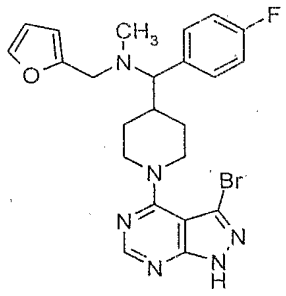
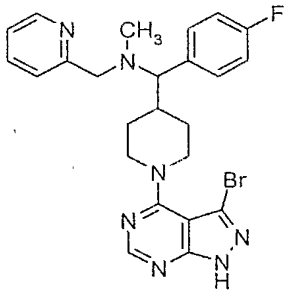
Entry	Name	Structure
94	4-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-4-(4-chlorophenyl)-N,N-dimethylbutan-1-amine	
95	3-bromo-4-(4-{(R)-(4-chlorophenyl)[(2-morpholin-4-ylethyl)oxy]methyl}piperidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine	
96	1-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-1-(4-fluorophenyl)-N-(furan-2-ylmethyl)-N-methylmethanamine	
97	1-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-1-(4-fluorophenyl)-N-methyl-N-(pyridin-2-ylmethyl)methanamine	

Table 1

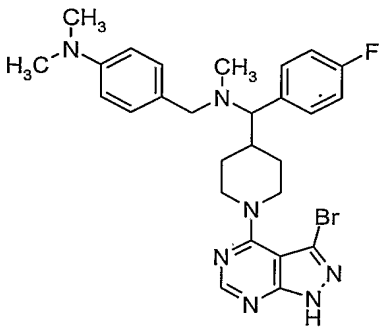
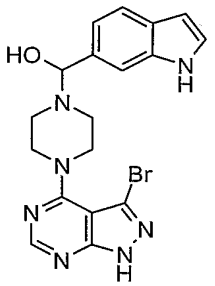
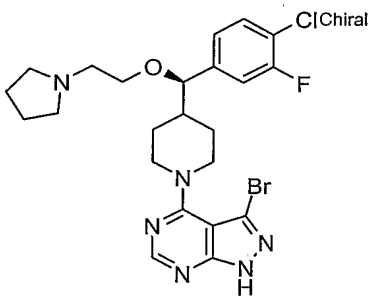
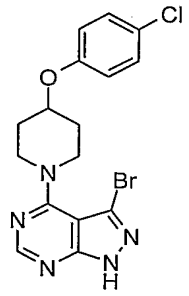
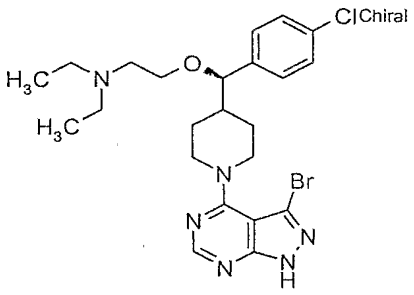
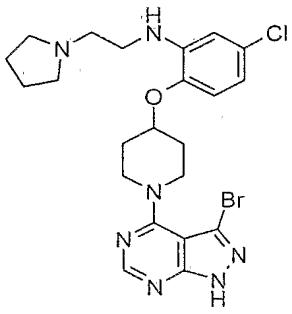
Entry	Name	Structure
98	4-{[{[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-fluorophenyl)methyl}(methyl)amino]methyl}-N,N-dimethylaniline	
99	[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl](1H-indol-6-yl)methanol	
100	3-bromo-4-(4-{(R)-(4-chloro-3-fluorophenyl)[(2-pyrrolidin-1-ylethyl)oxy]methyl}piperidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine	
101	3-bromo-4-{4-[(4-chlorophenyl)oxy]piperidin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	

Table 1

Entry	Name	Structure
102	2-{[(R)-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]oxy}-N,N-diethylethanamine	
103	2-{[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]oxy}-5-chloro-N-(2-pyrrolidin-1-ylethyl)aniline	

[0072] Another aspect of the invention is a pharmaceutical composition comprising the compound according to any one of paragraphs [0024]-[0071] and a pharmaceutically acceptable carrier.

[0073] Another aspect of the invention is a metabolite of the compound or the pharmaceutical composition according to any one of paragraphs [0024]-[0072].

[0074] Another aspect of the invention is a method of modulating the *in vivo* activity of a kinase, the method comprising administering to a subject an effective amount of a composition comprising at least one of: the compound according to any of paragraphs [0024]-[0071], the pharmaceutical composition according to paragraph [0072], a compound explicitly provided against in paragraph [0025], and a pharmaceutical composition comprising a compound, the composition of which was, explicitly provided against in paragraph [0025] and a pharmaceutically acceptable carrier.

[0075] Another aspect of the invention is the method according to paragraph [0074], wherein the kinase is p70S6, Akt-1 and/or Akt-2 kinase.

[0076] Another aspect of the invention is the method according to paragraph [0075], wherein modulating the *in vivo* activity of a kinase comprises inhibition of the kinase.

[0077] Another aspect of the invention is a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities, the method comprising administering, to a mammal in need thereof, a therapeutically effective amount of a composition comprising at least one of: the compound according to any of paragraphs [0024]-[0071], the pharmaceutical composition according to paragraph [0072], a compound explicitly provided against in paragraph [0025], and a pharmaceutical composition comprising a compound explicitly provided against in paragraph [0025] and a pharmaceutically acceptable carrier.

[0078] Another aspect of the invention is a method of screening for modulator of a kinase, preferably p70S6K, Akt-1 and/or Akt-2 kinase, the method comprising combining at least one of: the compound according to any of paragraphs [0024]-[0071], the pharmaceutical composition according to paragraph [0072], a compound explicitly provided against in paragraph [0025], and a pharmaceutical composition comprising a compound explicitly provided against in paragraph [0025] and a pharmaceutically acceptable carrier, and at least one candidate agent and a kinase and determining the effect of the candidate agent on the activity of said kinase.

[0079] Another aspect of the invention is a method of inhibiting proliferative activity in a cell, the method comprising administering an effective amount of: the compound according to any of paragraphs [0024]-[0071], the pharmaceutical composition according to paragraph [0072], a compound explicitly provided against in paragraph [0025], and a pharmaceutical composition comprising a compound explicitly provided against in paragraph [0022] and a pharmaceutically acceptable carrier.

[0080] Another aspect of the invention is a method of inhibiting abnormal metabolic activity in a cell, the method comprising administering an effective amount of: the compound according to any of paragraphs [0024]-[0071], the pharmaceutical composition according to paragraph [0072], a compound explicitly provided against in paragraph [0025], and a pharmaceutical

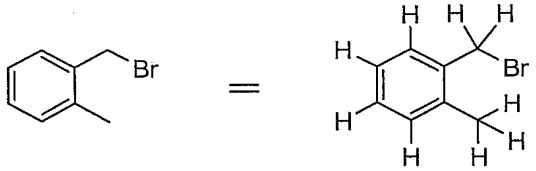
composition comprising a compound explicitly provided against in paragraph [0025] and a pharmaceutically acceptable carrier.

Definitions

[0081] As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise or they are expressly defined to mean something different.

[0082] The symbol "-" means a single bond, "=" means a double bond, "≡" means a triple bond. The symbol "∿∿∿" refers to a group on a double-bond as occupying either position on the terminus of a double bond to which the symbol is attached; that is, the geometry, *E*- or *Z*-, of the double bond is ambiguous. When a group is depicted removed from its parent formula, the "∼" symbol will be used at the end of the bond which was theoretically cleaved in order to separate the group from its parent structural formula.

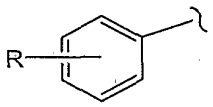
[0083] When chemical structures are depicted or described, unless explicitly stated otherwise, all carbons are assumed to have hydrogen substitution to conform to a valence of four. For example, in the structure on the left-hand side of the schematic below there are nine hydrogens implied. The nine hydrogens are depicted in the right-hand structure. Sometimes a particular atom in a structure is described in textual formula as having a hydrogen or hydrogens as substitution (expressly defined hydrogen), for example, $-CH_2CH_2-$. It is understood by one of ordinary skill in the art that the aforementioned descriptive techniques are common in the chemical arts to provide brevity and simplicity to description of otherwise complex structures.



[0084] In this application, some ring structures are depicted generically and will be described textually. For example, in the schematic below, if in the structure on the left, ring A is used to describe a "spirocyclyl," then if ring A is cyclopropyl, there are at most four hydrogens on

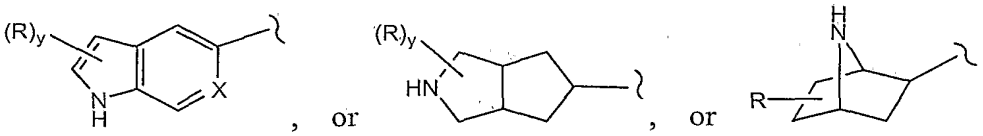
ring A (when "R" can also be -H). In another example, as depicted on the right side of the schematic below, if ring B is used to describe a "phenylene" then there can be at most four hydrogens on ring B (assuming depicted cleaved bonds are not C-H bonds).

[0085] If a group "R" is depicted as "floating" on a ring system, as for example in the formula:



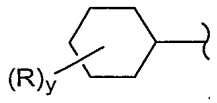
then, unless otherwise defined, a substituent "R" may reside on any atom of the ring system, assuming replacement of a depicted, implied, or expressly defined hydrogen from one of the ring atoms, so long as a stable structure is formed.

[0086] If a group "R" is depicted as floating on a fused ring system, as for example in the formulae:

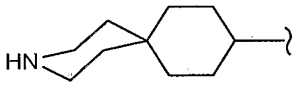


then, unless otherwise defined, a substituent "R" may reside on any atom of the fused ring system, assuming replacement of a depicted hydrogen (for example the -NH- in the formula above), implied hydrogen (for example as in the formula above, where the hydrogens are not shown but understood to be present), or expressly defined hydrogen (for example where in the formula above, "X" equals =CH-) from one of the ring atoms, so long as a stable structure is formed. In the example depicted, the "R" group may reside on either the 5-membered or the 6-membered ring of the fused ring system. In the formula depicted above, when y is 2 for example, then the two "R's" may reside on any two atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

[0087] When a group "R" is depicted as existing on a ring system containing saturated carbons, as for example in the formula:



where, in this example, "y" can be more than one, assuming each replaces a currently depicted, implied, or expressly defined hydrogen on the ring; then, unless otherwise defined, where the resulting structure is stable, two "R's" may reside on the same carbon. A simple example is when R is a methyl group; there can exist a geminal dimethyl on a carbon of the depicted ring (an "annular" carbon). In another example, two R's on the same carbon, including that carbon, may form a ring, thus creating a spirocyclic ring (a "spirocyclyl" group) structure with the depicted ring as for example in the formula:



[0088] "Alkyl" is intended to include linear, branched, or cyclic hydrocarbon structures and combinations thereof, inclusively. For example, "C_8 alkyl" may refer to an *n*-octyl, *iso*-octyl, cyclohexylethyl, and the like. Lower alkyl refers to alkyl groups of from one to six carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *s*-butyl, *t*-butyl, isobutyl, pentyl, hexyl and the like. Higher alkyl refers to alkyl groups containing more that eight carbon atoms. Exemplary alkyl groups are those of C_{20} or below. Cycloalkyl is a subset of alkyl and includes cyclic hydrocarbon groups of from three to thirteen carbon atoms. Examples of cycloalkyl groups include c-propyl, c-butyl, c-pentyl, norbornyl, adamantyl and the like. In this application, alkyl refers to alkanyl, alkenyl, and alkynyl residues (and combinations thereof); it is intended to include cyclohexylmethyl, vinyl, allyl, isoprenyl, and the like. Thus, when an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of *carbons* are intended to be encompassed; thus, for example, either "butyl" or "C_4alkyl" is meant to include *n*-butyl, *sec*-butyl, isobutyl, *t*-butyl, isobutenyl and but-2-yne radicals; and for example, "propyl" or "C_3alkyl" each include *n*-propyl, propenyl, and isopropyl. Otherwise, if alkenyl and/or alkynyl descriptors *are used* in a particular definition of a group, for example "C_4alkyl" along "C_4alkenyl," then C_4alkenyl geometric isomers are not meant to be included in "C_4alkyl," but other 4-carbon isomers are, for example C_4alkynyl. For example, a more general description, intending to encompass the invention as a whole may describe a particular group as

"C_{1-8}alkyl" while a preferred species may describe the same group as including, "C_{1-8}alkyl," "C_{1-6}alkenyl" and "C_{1-5}alkynyl."

[0089] "Alkylene" refers to straight or branched chain divalent radical consisting solely of carbon and hydrogen atoms, containing no unsaturation and having from one to ten carbon atoms, for example, methylene, ethylene, propylene, *n*-butylene and the like. Alkylene is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and, specifically, fully saturated. Examples of alkylene include ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$), dimethylpropylene ($-CH_2C(CH_3)_2CH_2-$), and cyclohexylpropylene ($-CH_2CH_2CH(C_6H_{13})$).

[0090] "Alkylidene" refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms, having from two to ten carbon atoms, for example, ethylidene, propylidene, *n*-butylidene, and the like. Alkylidene is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and, specifically, double bond unsaturation. The unsaturation present includes at least one double bond.

[0091] "Alkylidyne" refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms having from two to ten carbon atoms, for example, propylid-2-ynyl, *n*-butylid-1-ynyl, and the like. Alkylidyne is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and, specifically, triple bond unsaturation. The unsaturation present includes at least one triple bond.

[0092] Any of the above radicals, "alkylene," "alkylidene" and "alkylidyne," when optionally substituted, may contain alkyl substitution which itself contains unsaturation. For example, 2-(2-phenylethynyl-but-3-enyl)-naphthalene (IUPAC name) contains an *n*-butylid-3-ynyl radical with a vinyl substituent at the 2-position of said radical.

[0093] "Alkoxy" or "alkoxyl" refers to the group -O-alkyl, for example including from one to eight carbon atoms of a straight, branched, cyclic configuration, unsaturated chains, and combinations thereof attached to the parent structure through an oxygen atom. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like. Lower-alkoxy refers to groups containing one to six carbons.

[0094] "Substituted alkoxy" refers to the group -O-(substituted alkyl), the substitution on the alkyl group generally containing more than only carbon (as defined by alkoxy). One exemplary substituted alkoxy group is "polyalkoxy" or -O-optionally substituted alkylene-optionally substituted alkoxy, and includes groups such as $-OCH_2CH_2OCH_3$, and glycol ethers such as polyethyleneglycol and $-O(CH_2CH_2O)_xCH_3$, where x is an integer of between about two and about twenty, in another example, between about two and about ten, and in a further example between about two and about five. Another exemplary substituted alkoxy group is hydroxyalkoxy or $-OCH_2(CH_2)_yOH$, where y is for example an integer of between about one and about ten, in another example y is an integer of between about one and about four.

[0095] "Acyl" refers to groups of from one to ten carbon atoms of a straight, branched, cyclic configuration, saturated, unsaturated and aromatic and combinations thereof, attached to the parent structure through a carbonyl functionality. One or more carbons in the acyl residue may be replaced by nitrogen, oxygen or sulfur as long as the point of attachment to the parent remains at the carbonyl. Examples include acetyl, benzoyl, propionyl, isobutyryl, *t*-butoxycarbonyl, benzyloxycarbonyl and the like. Lower-acyl refers to groups containing one to six carbons.

[0096] "α-Amino Acids" refer to naturally occurring and commercially available amino acids and optical isomers thereof. Typical natural and commercially available α-amino acids are glycine, alanine, serine, homoserine, threonine, valine, norvaline, leucine, isoleucine, norleucine, aspartic acid, glutamic acid, lysine, omithine, histidine, arginine, cysteine, homocysteine, methionine, phenylalanine, homophenylalanine, phenylglycine, ortho-tyrosine, meta-tyrosine, para-tyrosine, tryptophan, glutamine, asparagine, proline and hydroxyproline. A "side chain of an α-amino acid" refers to the radical found on the α-carbon of an α-amino acid as defined above, for example, hydrogen (for glycine), methyl (for alanine), benzyl (for phenylalanine), and the like.

[0097] "Amino" refers to the group $-NH_2$. "Substituted amino," refers to the group -N(H)R or –N(R)R where each R is independently selected from the group: optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted heterocyclyl,

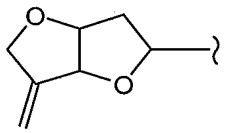
acyl, carboxy, alkoxycarbonyl, sulfanyl, sulfinyl and sulfonyl, for example, diethylamino, methylsulfonylamino, and furanyl-oxy-sulfonamino.

[0098] "Aryl" refers to aromatic six- to fourteen-membered carbocyclic ring, for example, benzene, naphthalene, indane, tetralin, fluorene and the like, univalent radicals. As univalent radicals, the aforementioned ring examples are named, phenyl, naphthyl, indanyl, tetralinyl, and fluorenyl.

[0099] "Arylene" generically refers to any aryl that has at least two groups attached thereto. For a more specific example, "phenylene" refers to a divalent phenyl ring radical. A phenylene, thus may have more than two groups attached, but is defined by a minimum of two non-hydrogen groups attached thereto.

[0100] "Arylalkyl" refers to a residue in which an aryl moiety is attached to a parent structure via one of an alkylene, alkylidene, or alkylidyne radical. Examples include benzyl, phenethyl, phenylvinyl, phenylallyl and the like. Both the aryl, and the corresponding alkylene, alkylidene, or alkylidyne radical portion of an arylalkyl group may be optionally substituted. "Lower arylalkyl" refers to an arylalkyl where the "alkyl" portion of the group has one to six carbons; this can also be refered to as C_{1-6} arylalkyl.

[0101] "Exo-alkenyl" refers to a double bond that emanates from an annular carbon, and is not within the ring system, for example the double bond depicted in the formula below.



[0102] In some examples, as appreciated by one of ordinary skill in the art, two adjacent groups on an aromatic system may be fused together to form a ring structure. The fused ring structure may contain heteroatoms and may be optionally substituted with one or more groups. It should additionally be noted that saturated carbons of such fused groups (i.e. saturated ring structures) can contain two substitution groups.

[0103] "Fused-polycyclic" or "fused ring system" refers to a polycyclic ring system that contains bridged or fused rings; that is, where two rings have more than one shared atom in their ring structures. In this application, fused-polycyclics and fused ring systems are not

necessarily all aromatic ring systems. Typically, but not necessarily, fused-polycyclics share a vicinal set of atoms, for example naphthalene or 1,2,3,4-tetrahydro-naphthalene. A spiro ring system is not a fused-polycyclic by this definition, but fused polycyclic ring systems of the invention may themselves have spiro rings attached thereto via a single ring atom of the fused-polycyclic.

[0104] "Halogen" or "halo" refers to fluorine, chlorine, bromine or iodine. "Haloalkyl" and "haloaryl" refer generically to alkyl and aryl radicals that are substituted with one or more halogens, respectively. Thus, "dihaloaryl," "dihaloalkyl," "trihaloaryl" etc. refer to aryl and alkyl substituted with a plurality of halogens, but not necessarily a plurality of the same halogen; thus 4-chloro-3-fluorophenyl is within the scope of dihaloaryl.

[0105] "Heteroarylene" generically refers to any heteroaryl that has at least two groups attached thereto. For a more specific example, "pyridylene" refers to a divalent pyridyl ring radical. A pyridylene, thus may have more than two groups attached, but is defined by a minimum of two non-hydrogen groups attached thereto.

[0106] "Heteroatom" refers to O, S, N, or P.

[0107] "Heterocyclyl" refers to a stable three- to fifteen-membered ring radical that consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclyl radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused or bridged ring systems as well as spirocyclic systems; and the nitrogen, phosphorus, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidized to various oxidation states. In a specific example, the group $-S(O)_{0-2}-$, refers to -S- (sulfide), -S(O)- (sulfoxide), and $-SO_2-$ (sulfone). For convenience, nitrogens, particularly but not exclusively, those defined as annular aromatic nitrogens, are meant to include their corresponding *N*-oxide form, although not explicitly defined as such in a particular example. Thus, for a compound of the invention having, for example, a pyridyl ring; the corresponding pyridyl-*N*-oxide is meant to be included as another compound of the invention. In addition, annular nitrogen atoms may be optionally quaternized; and the ring radical may be partially or fully saturated or aromatic. Examples of heterocyclyl radicals include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofuranyl, carbazoyl, cinnolinyl, dioxolanyl, indolizinyl, naphthyridinyl,

perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazoyl, tetrahydroisoquinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, dihydropyridinyl, tetrahydropyridinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxazolidinyl, triazolyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothieliyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, dioxaphospholanyl, and oxadiazolyl.

[0108] "Heteroalicyclic" refers specifically to a non-aromatic heterocyclyl radical. A heteroalicyclic may contain unsaturation, but is not aromatic.

[0109] "Heteroaryl" refers specifically to an aromatic heterocyclyl radical.

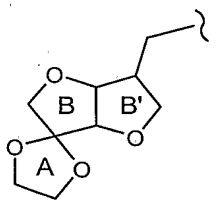
[0110] "Heterocyclylalkyl" refers to a residue in which a heterocyclyl is attached to a parent structure via one of an alkylene, alkylidene, or alkylidyne radical. Examples include (4-methylpiperazin-1-yl) methyl, (morpholin-4-yl) methyl, (pyridine-4-yl) methyl, 2-(oxazolin-2-yl) ethyl, 4-(4-methylpiperazin-1-yl)-2-butenyl, and the like. Both the heterocyclyl, and the corresponding alkylene, alkylidene, or alkylidyne radical portion of a heterocyclylalkyl group may be optionally substituted. "Lower heterocyclylalkyl" refers to a heterocyclylalkyl where the "alkyl" portion of the group has one to six carbons. "Heteroalicyclylalkyl" refers specifically to a heterocyclylalkyl where the heterocyclyl portion of the group is non-aromatic; and "heteroarylalkyl" refers specifically to a heterocyclylalkyl where the heterocyclyl portion of the group is aromatic Such terms may be described in more than one way, for example, "lower heterocyclylalkyl" and "heterocyclyl C_{1-6}alkyl" are equivalent terms.

[0111] "Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. One of ordinary skill in the

art would understand that, with respect to any molecule described as containing one or more optional substituents, that only sterically practical and/or synthetically feasible compounds are meant to be included. "Optionally substituted" refers to all subsequent modifiers in a term, for example in the term "optionally substituted arylC_{1-8}alkyl," optional substitution may occur on one or both the "C_{1-8}alkyl" portion and the "aryl" portion of the molecule. A list of exemplary optional substitutions is included below in the definition of "substituted."

[0112] "Saturated bridged ring system" refers to a bicyclic or polycyclic ring system that is not aromatic. Such a system may contain isolated or conjugated unsaturation, but not aromatic or heteroaromatic rings in its core structure (but may have aromatic substitution thereon). For example, hexahydro-furo[3,2-b]furan, 2,3,3a,4,7,7a-hexahydro-1H-indene, 7-aza-bicyclo[2.2.1]heptane, and 1,2,3,4,4a,5,8,8a-octahydro-naphthalene are all included in the class "saturated bridged ring system.

[0113] "Spirocyclyl" or "spirocyclic ring" refers to a ring originating from a particular annular carbon of another ring. For example, as depicted below, a ring atom of a saturated bridged ring system (rings B and B'), but not a bridgehead atom, can be a shared atom between the saturated bridged ring system and a spirocyclyl (ring A) attached thereto. A spirocyclyl can be carbocyclic or heteroalicyclic.



[0114] "Substituted" alkyl, aryl, and heterocyclyl, refer respectively to alkyl, aryl, and heterocyclyl, wherein one or more (for example up to about five, in another example, up to about three) hydrogen atoms are replaced by a substituent independently selected from: alkyl (for example, fluoromethyl, hydroxypropyl, nitromethyl, aminoethyl and the like.), aryl (for example, 4-hydroxyphenyl, 2,3-difluorophenyl, and the like), arylalkyl (for example, 1-phenyl-ethyl, *para*-methoxyphenylethyl and the like), heterocyclylalkyl (for example, 1-pyridin-3-yl-ethyl, N-ethylmorphonlino and the like), heterocyclyl (for example, 5-chloro-pyridin-3-yl, 1-methyl-piperidin-4-yl and the like), alkoxy (for example methoxyethoxy, hydroxypropyloxy, methylenedioxy and the like), amino (for example, methylamino,

diethylamino, trifluoroacetylamino and the like), amidino, aryloxy (for example, phenoxy, *para*-chlorophenoxy, *meta*-aminophenoxy, *para*-phenoxyphenoxy and the like), arylalkyloxy (for example, benzyloxy, 3-chlorobenzyloxy, *meta*-phenoxybenzyloxy and the like), carboxy (-CO_2H), carboalkoxy (that is, acyloxy or -OC(=O)R), carboxyalkyl (that is, esters or -CO_2R), carboxamido, benzyloxycarbonylamino (CBZ-amino), cyano, acyl, halogen, hydroxy, nitro, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, thiol, halogen, hydroxy, oxo, carbamyl, acylamino, hydrazino, hydroxylamino, and sulfonamido.

[0115] "Sulfanyl" refers to the groups: -S-(optionally substituted alkyl), -S-(optionally substituted aryl), and -S-(optionally substituted heterocyclyl).

[0116] "Sulfinyl" refers to the groups: -S(O)-H, -S(O)-(optionally substituted alkyl), -S(O)-optionally substituted aryl), and -S(O)-(optionally substituted heterocyclyl).

[0117] "Sulfonyl" refers to the groups: -$S(O_2)$-H, -$S(O_2)$-(optionally substituted alkyl), -$S(O_2)$-optionally substituted aryl), -$S(O_2)$-(optionally substituted heterocyclyl), -$S(O_2)$-(optionally substituted alkoxy), -$S(O_2)$-optionally substituted aryloxy), and -$S(O_2)$-(optionally substituted heterocyclyloxy).

[0118] "Yield" for each of the reactions described herein is expressed as a percentage of the theoretical yield.

[0118] Some of the compounds of the invention may have imino, amino, oxo or hydroxy substituents off aromatic heterocyclyl systems. For purposes of this disclosure, it is understood that such imino, amino, oxo or hydroxy substituents may exist in their corresponding tautomeric form, i.e., amino, imino, hydroxy or oxo, respectively.

[0119] Compounds of the invention are named according to systematic application of the nomenclature rules agreed upon by the International Union of Pure and Applied Chemistry (IUPAC), International Union of Biochemistry and Molecular Biology (IUBMB), and the Chemical Abstracts Service (CAS).

[0120] The compounds of the invention, or their pharmaceutically acceptable salts, may have asymmetric carbon atoms, oxidized sulfur atoms or quaternized nitrogen atoms in their structure.

[0121] The compounds of the invention and their pharmaceutically acceptable salts may exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. The compounds may also exist as geometric isomers. All such single stereoisomers, racemates and mixtures thereof, and geometric isomers are intended to be within the scope of this invention.

[0122] It is assumed that when considering generic descriptions of compounds of the invention for the purpose of constructing a compound, such construction results in the creation of a stable structure. That is, one of ordinary skill in the art would recognize that there can theoretically be some constructs which would not normally be considered as stable compounds (that is, sterically practical and/or synthetically feasible, *supra*).

[0123] When a particular group with its bonding structure is denoted as being bonded to two partners; that is, a divalent radical, for example, $-OCH_2-$, then it is understood that either of the two partners may be bound to the particular group at one end, and the other partner is necessarily bound to the other end of the particular group, unless stated explicitly otherwise. Stated another way, divalent radicals are not to be construed as limited to the depicted orientation, for example "$-OCH_2-$" is meant to mean not only "$-OCH_2-$" as drawn, but also "$-CH_2O-$."

[0124] Methods for the preparation and/or separation and isolation of single stereoisomers from racemic mixtures or non-racemic mixtures of stereoisomers are well known in the art. For example, optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. Enantiomers (R- and S-isomers) may be resolved by methods known to one of ordinary skill in the art, for example by: formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallization; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallization, selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where a desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step may be required to liberate the desired enantiomeric form. Alternatively, specific enantiomer may be

synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting on enantiomer to the other by asymmetric transformation. For a mixture of enantiomers, enriched in a particular enantiomer, the major component enantiomer may be further enriched (with concomitant loss in yield) by recrystallization.

[0125] "Patient" for the purposes of the present invention includes humans and other animals, particularly mammals, and other organisms. Thus the methods are applicable to both human therapy and veterinary applications. In a preferred embodiment the patient is a mammal, and in a most preferred embodiment the patient is human.

[0126] "Kinase-dependent diseases or conditions" refer to pathologic conditions that depend on the activity of one or more protein kinases. Kinases either directly or indirectly participate in the signal transduction pathways of a variety of cellular activities including proliferation, adhesion, migration, differentiation and invasion. Diseases associated with kinase activities include tumor growth, the pathologic neovascularization that supports solid tumor growth, and associated with other diseases where excessive local vascularization is involved such as ocular diseases (diabetic retinopathy, age-related macular degeneration, and the like) and inflammation (psoriasis, rheumatoid arthritis, and the like).

[0127] While not wishing to be bound to theory, phosphatases can also play a role in "kinase-dependent diseases or conditions" as cognates of kinases; that is, kinases phosphorylate and phosphatases dephosphorylate, for example protein substrates. Therefore compounds of the invention, while modulating kinase activity as described herein, may also modulate, either directly or indirectly, phosphatase activity. This additional modulation, if present, may be synergistic (or not) to activity of compounds of the invention toward a related or otherwise interdependent kinase or kinase family. In any case, as stated previously, the compounds of the invention are useful for treating diseases characterized in part by abnormal levels of cell metabolism, proliferation (i.e. tumor growth), programmed cell death (apoptosis), cell migration and invasion and angiogenesis associated with tumor growth.

[0128] "Therapeutically effective amount" is an amount of a compound of the invention, that when administered to a patient, ameliorates a symptom of the disease. The amount of a compound of the invention which constitutes a "therapeutically effective amount" will vary depending on the compound, the disease state and its severity, the age of the patient to be

treated, and the like. The therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

[0129] "Cancer" refers to cellular-proliferative disease states, including but not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hanlartoma, inesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [neplrroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformians), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, SertoliLeydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial

carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma], fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal lands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

[0130] "Pharmaceutically acceptable acid addition salt" refers to those salts that retain the biological effectiveness of the free bases and that are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, as well as organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

[0131] "Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Exemplary salts are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins, and the like. Exemplary organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine. (See, for example, S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19 which is incorporated herein by reference.)

[0132] "Prodrug" refers to compounds that are transformed (typically rapidly) *in vivo* to yield the parent compound of the above formulae, for example, by hydrolysis in blood. Common examples include, but are not limited to, ester and amide forms of a compound having an active form bearing a carboxylic acid moiety. Examples of pharmaceutically acceptable esters of the compounds of this invention include, but are not limited to, alkyl esters (for example with between about one and about six carbons) wherein the alkyl group is a straight or branched chain. Acceptable esters also include cycloalkyl esters and arylalkyl esters such as, but not limited to benzyl. Examples of pharmaceutically acceptable amides of the compounds of this invention include, but are not limited to, primary amides, and secondary and tertiary alkyl amides (for example with between about one and about six carbons). Amides and esters of the compounds of the present invention may be prepared according to conventional methods. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference for all purposes.

[0133] "Metabolite" refers to the break-down or end product of a compound or its salt produced by metabolism or biotransformation in the animal or human body; for example, biotransformation to a more polar molecule such as by oxidation, reduction, or hydrolysis, or to a conjugate (see Goodman and Gilman, "The Pharmacological Basis of Therapeutics" 8.sup.th Ed., Pergamon Press, Gilman et al. (eds), 1990 for a discussion of biotransformation). As used herein, the metabolite of a compound of the invention or its salt may be the biologically active form of the compound in the body. In one example, a prodrug may be used such that the biologically active form, a metabolite, is released *in vivo*. In another example, a biologically active metabolite is discovered serendipitously, that is, no prodrug design *per se* was undertaken. An assay for activity of a metabolite of a compound of the present invention is known to one of skill in the art in light of the present disclosure.

[0134] In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

[0135] In addition, it is intended that the present invention cover compounds made either using standard organic synthetic techniques, including combinatorial chemistry or by biological methods, such as bacterial digestion, metabolism, enzymatic conversion, and the like.

[0136] "Treating" or "treatment" as used herein covers the treatment of a disease-state in a human, which disease-state is characterized by abnormal cellular proliferation and/or invasion, or metabolism and includes at least one of: (i) preventing the disease-state from occurring in a human, in particular, when such human is predisposed to the disease-state but has not yet been diagnosed as having it; (ii) inhibiting the disease-state, i.e., arresting its development; and (iii) relieving the disease-state, i.e., causing regression of the disease-state. As is known in the art, adjustments for systemic versus localized delivery, age, body weight, general health, sex, diet, time of administration, drug interaction and the severity of the condition may be necessary, and will be ascertainable with routine experimentation by one of ordinary skill in the art.

[0137] One of ordinary skill in the art would understand that certain crystallized, protein-ligand complexes, in particular p70S6K-ligand complexes, and their corresponding x-ray structure coordinates can be used to reveal new structural information useful for understanding the biological activity of kinases as described herein. As well, the key structural features of the aforementioned proteins, particularly, the shape of the ligand binding site, are useful in methods for designing or identifying selective modulators of kinases and in solving the structures of other proteins with similar features. Such protein-ligand complexes, having compounds of the invention as their ligand component, are an aspect of the invention.

[0138] As well, one of ordinary skill in the art would appreciate that such suitable x-ray quality crystals can be used as part of a method of identifying a candidate agent capable of binding to and modulating the activity of kinases. Such methods may be characterized by the following aspects: a) introducing into a suitable computer program, information defining a ligand binding domain of a kinase in a conformation (e.g. as defined by x-ray structure coordinates obtained from suitable x-ray quality crystals as described above) wherein the computer program creates a model of the three dimensional structures of the ligand binding domain, b) introducing a model of the three dimensional structure of a candidate agent in the computer program, c) superimposing the model of the candidate agent on the model of the ligand binding domain, and d) assessing whether the candidate agent model fits spatially into the ligand binding

domain. Aspects a-d are not necessarily carried out in the aforementioned order. Such methods may further entail: performing rational drug design with the model of the three-dimensional structure, and selecting a potential candidate agent in conjunction with computer modeling.

[0139] Additionally, one skilled in the art would appreciate that such methods may further entail: employing a candidate agent, so-determined to fit spatially into the ligand binding domain, in a biological activity assay for kinase modulation, and determining whether said candidate agent modulates kinase activity in the assay. Such methods may also include administering the candidate agent, determined to modulate kinase activity, to a mammal suffering from a condition treatable by kinase modulation, such as those described above.

[0140] Also, one skilled in the art would appreciate that compounds of the invention can be used in a method of evaluating the ability of a test agent to associate with a molecule or molecular complex comprising a ligand binding domain of a kinase. Such a method may be characterized by the following aspects: a) creating a computer model of a kinase binding pocket using structure coordinates obtained from suitable x-ray quality crystals of the kinase, b) employing computational algorithms to perform a fitting operation between the test agent and the computer model of the binding pocket, and c) analyzing the results of the fitting operation to quantify the association between the test agent and the computer model of the binding pocket.

General Administration

[0141] Administration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravesically, intracistemally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages.

[0142] The compositions will include a conventional pharmaceutical carrier or excipient and a compound of the invention as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc. Compositions of the invention may be used in combination with anticancer or other agents that are generally administered to a patient being treated for cancer. Adjuvants include preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0143] If desired, a pharmaceutical composition of the invention may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylalted hydroxytoluene, etc.

[0144] Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

[0145] One preferable route of administration is oral, using a convenient daily dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.

[0146] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b)

binders, as for example, cellulose derivatives, starch, alignates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

[0147] Solid dosage forms as described above can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain pacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedded compositions that can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

[0148] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. Such dosage forms are prepared, for example, by dissolving, dispersing, etc., a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like; solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide; oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan; or mixtures of these substances, and the like, to thereby form a solution or suspension.

[0149] Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

[0150] Compositions for rectal administrations are, for example, suppositories that can be prepared by mixing the compounds of the present invention with for example suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt while in a suitable body cavity and release the active component therein.

[0151] Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

[0152] Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and 99% to 1% by weight of a suitable pharmaceutical excipient. In one example, the composition will be between about 5% and about 75% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, with the rest being suitable pharmaceutical excipients.

[0153] Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, for treatment of a disease-state in accordance with the teachings of this invention.

[0154] The compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of the compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular disease-states, and the host undergoing therapy. The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kilograms, a dosage in the

range of about 0.01 to about 100 mg per kilogram of body weight per day is an example. The specific dosage used, however, can vary. For example, the dosage can depend on a number of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well known to one of ordinary skill in the art.

Utility of compounds of the invention as screening agents

[0155] To employ the compounds of the invention in a method of screening for candidate agents that bind to, for example p70S6K receptor kinase, the protein is bound to a support, and a compound of the invention is added to the assay. Alternatively, the compound of the invention is bound to the support and the protein is added. Classes of candidate agents among which novel binding agents may be sought include specific antibodies, non-natural binding agents identified in screens of chemical libraries, peptide analogs, etc. Of particular interest are screening assays for candidate agents that have a low toxicity for human cells. A wide variety of assays may be used for this purpose, including labeled *in vitro* protein-protein binding assays, electrophoretic mobility shift assays, immunoassays for protein binding, functional assays (phosphorylation assays, etc.) and the like.

[0156] The determination of the binding of the candidate agent to, for example, p70S6K protein may be done in a number of ways. In one example, the candidate agent (the compound of the invention) is labeled, for example, with a fluorescent or radioactive moiety and binding determined directly. For example, thus may be done by attaching all or a portion of the p70S6K protein to a solid support, adding a labeled agent (for example a compound of the invention in which at least one atom has been replaced by a detectable isotope), washing off excess reagent, and determining whether the amount of the label is that present on the solid support. Various blocking and washing steps may be utilized as is known in the art.

[0157] By "labeled" herein is meant that the compound is either directly or indirectly labeled with a label which provides a detectable signal, for example, radioisotope, fluorescent tag, enzyme, antibodies, particles such as magnetic particles, chemiluminescent tag, or specific binding molecules, and the like. Specific binding molecules include pairs, such as biotin and streptavidin, digoxin and antidigoxin, and the like. For the specific binding members, the

complementary member would normally be labeled with a molecule which provides for detection, in accordance with known procedures, as outlined above. The label can directly or indirectly provide a detectable signal.

[0158] In some embodiments, only one of the components is labeled. For example, p70S6K protein may be labeled at tyrosine positions using ^{125}I, or with fluorophores. Alternatively, more than one component may be labeled with different labels; using ^{125}I for the proteins, for example, and a fluorophor for the candidate agents.

[0159] The compounds of the invention may also be used as competitors to screen for additional drug candidates. "candidate bioactive agent" or "drug candidate" or grammatical equivalents as used herein describe any molecule, e.g., protein, oligopeptide, small organic molecule, polysaccharide, polynucleotide, etc., to be tested for bioactivity. They may be capable of directly or indirectly altering the cellular proliferation or metabolic phenotype or the expression of a cellular proliferation or metabolic sequence, including both nucleic acid sequences and protein sequences. In other cases, alteration of cellular proliferation or metabolic protein binding and/or activity is screened. In the case where protein binding or activity is screened, some embodiments exclude molecules already known to bind to that particular protein. Exemplary embodiments of assays described herein include candidate agents, which do not bind the target protein in its endogenous native state, termed herein as "exogenous" agents. In one example, exogenous agents further exclude antibodies to p70S6K.

[0160] Candidate agents can encompass numerous chemical classes, though typically they are organic molecules having a molecular weight of more than about 100 and less than about 2,500 daltons. Candidate agents comprise functional groups necessary for structural interaction with proteins, particularly hydrogen bonding and lipophilic binding, and typically include at least an amine, carbonyl, hydroxyl, ether, or carboxyl group, for example at least two of the functional chemical groups. The candidate agents often comprise cyclical carbon or heterocyclyl structures and/or aromatic or polyaromatic structures substituted with one or more of the above functional groups. Candidate agents are also found among biomolecules including peptides, saccharides, fatty acids, steroids, purines, pyrimidines, derivatives, structural analogs, or combinations thereof.

[0161] Candidate agents are obtained from a wide variety of sources including libraries of synthetic or natural compounds. For example, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural or synthetically produced libraries and compounds are readily modified through conventional chemical, physical and biochemical means. Known pharmacological agents may be subjected to directed or random chemical modifications, such as acylation, alkylation, esterification, amidification to produce structural analogs.

[0162] In one example, the binding of the candidate agent is determined through the use of competitive binding assays. In this example, the competitor is a binding moiety known to bind to p70S6K, such as an antibody, peptide, binding partner, ligand, etc. Under certain circumstances, there may be competitive binding as between the candidate agent and the binding moiety, with the binding moiety displacing the candidate agent.

[0163] In some embodiments, the candidate agent is labeled. Either the candidate agent, or the competitor, or both, is added first to p70S6K protein for a time sufficient to allow binding, if present. Incubations may be performed at any temperature that facilitates optimal activity, typically between 4°C and 40°C.

[0164] Incubation periods are selected for optimum activity, but may also be optimized to facilitate rapid high throughput screening. Typically between 0.1 and 1 hour will be sufficient. Excess reagent is generally removed or washed away. The second component is then added, and the presence or absence of the labeled component is followed, to indicate binding.

[0165] In one example, the competitor is added first, followed by the candidate agent. Displacement of the competitor is an indication the candidate agent is binding to p70S6K and thus is capable of binding to, and potentially modulating, the activity of the p70S6K. In this embodiment, either component can be labeled. Thus, for example, if the competitor is labeled, the presence of label in the wash solution indicates displacement by the agent. Alternatively, if the candidate agent is labeled, the presence of the label on the support indicates displacement.

[0166] In an alternative embodiment, the candidate agent is added first, with incubation and washing, followed by the competitor. The absence of binding by the competitor may indicate

the candidate agent is bound to p70S6K with a higher affinity. Thus, if the candidate agent is labeled, the presence of the label on the support, coupled with a lack of competitor binding, may indicate the candidate agent is capable of binding to p70S6K.

[0167] It may be of value to identify the binding site of p70S6K. This can be done in a variety of ways. In one embodiment, once p70S6K has been identified as binding to the candidate agent, the p70S6K is fragmented or modified and the assays repeated to identify the necessary components for binding.

[0168] Modulation is tested by screening for candidate agents capable of modulating the activity of p70S6K comprising the steps of combining a candidate agent with p70S6K, as above, and determining an alteration in the biological activity of the p70S6K. Thus, in this embodiment, the candidate agent should both bind to (although this may not be necessary), and alter its biological or biochemical activity as defined herein. The methods include both *in vitro* screening methods and *in vivo* screening of cells for alterations in cell viability, morphology, and the like.

[0169] Alternatively, differential screening may be used to identify drug candidates that bind to native p70S6K, but cannot bind to modified p70S6K.

[0170] Positive controls and negative controls can be used in the assays. For example, all control and test samples are performed in at least triplicate to obtain statistically significant results. Incubation of samples is for a time sufficient for the binding of the agent to the protein. Following incubation, samples are washed free of non-specifically bound material and the amount of bound, generally labeled agent determined. For example, where a radiolabel is employed, the samples can be counted in a scintillation counter to determine the amount of bound compound.

[0171] A variety of other reagents can be included in the screening assays. These include reagents like salts, neutral proteins, e.g., albumin, detergents, etc which may be used to facilitate optimal protein-protein binding and/or reduce non-specific or background interactions. Also reagents that otherwise improve the efficiency of the assay, such as protease inhibitors, nuclease inhibitors, anti-microbial agents, etc., may be used. The mixture of components can be added in any order that provides for the requisite binding.

[0172] One of ordinary skill in the art would understand that certain crystallized, protein-ligand complexes, in particular p70S6K -ligand complexes, and their corresponding x-ray structure coordinates can be used to reveal new structural information useful for understanding the biological activity of p70S6 kinase's as described herein. As well, the key structural features of the aforementioned proteins, particularly, the shape of the ligand binding site, are useful in methods for designing or identifying selective modulators of p70S6 kinase's and in solving the structures of other proteins with similar features. Ligands of such complexes may include compounds of the invention as described herein.

[0173] As well, one of ordinary skill in the art would appreciate that such suitable x-ray quality crystals can be used as part of a method of identifying a candidate agent capable of binding to and modulating the activity of p70S6 kinases. Such methods may be characterized by the following aspects: a) introducing into a suitable computer program, information defining a ligand binding domain of a p70S6 kinase in a conformation (e.g. as defined by x-ray structure coordinates obtained from suitable x-ray quality crystals as described above) wherein the computer program creates a model of the three dimensional structures of the ligand binding domain, b) introducing a model of the three dimensional structure of a candidate agent in the computer program, c) superimposing the model of the candidate agent on the model of the ligand binding domain, and d) assessing whether the candidate agent model fits spatially into the ligand binding domain. Aspects a-d are not necessarily carried out in the aforementioned order. Such methods may further entail: performing rational drug design with the model of the three-dimensional structure, and selecting a potential candidate agent in conjunction with computer modeling.

[0174] Additionally, one skilled in the art would appreciate that such methods may further entail: employing a candidate agent, so-determined to fit spatially into the ligand binding domain, in a biological activity assay for p70S6 kinase modulation, and determining whether said candidate agent modulates p70S6 kinase activity in the assay. Such methods may also include administering the candidate agent, determined to modulate p70S6 kinase activity, to a mammal suffering from a condition treatable by p70S6 kinase modulation, such as those described above.

[0175] Also, one skilled in the art would appreciate that compounds of the invention can be used in a method of evaluating the ability of a test agent to associate with a molecule or molecular complex comprising a ligand binding domain of a p70S6 kinase. Such a method may be characterized by the following aspects: a) creating a computer model of a p70S6 kinase binding pocket using structure coordinates obtained from suitable x-ray quality crystals of the p70S6 kinase, b) employing computational algorithms to perform a fitting operation between the test agent and the computer model of the binding pocket, and c) analyzing the results of the fitting operation to quantify the association between the test agent and the computer model of the binding pocket.

Abbreviations and their Definitions

[0176] The following abbreviations and terms have the indicated meanings throughout:

Abbreviation	Meaning
Ac	acetyl
ACN	acetonitrile
ATP	adenosine triphosphate
BNB	4-bromomethyl-3-nitrobenzoic acid
Boc	t-butyloxy carbonyl
br	broad
Bu	butyl
°C	degrees Celsius
c-	cyclo
CBZ	CarboBenZoxy = benzyloxycarbonyl
d	doublet
dd	doublet of doublet
dt	doublet of triplet
DBU	Diazabicyclo[5.4.0]undec-7-ere
DCM	dichloromethane = methylene chloride = CH_2Cl_2
DCE	dichloroethylene

Abbreviation	Meaning
DEAD	diethyl azodicarboxylate
DIC	diisopropylcarbodiimide
DIEA	N,N-diisopropylethyl amine
DMAP	4-N,N-dimethylaminopyridine
DMF	N,N-dimethylfonnamide
DMSO	dimethyl sulfoxide
DVB	1,4-divinylbenzene
EEDQ	2-ethoxy-l-ethoxycarbonyl-1,2-dihydroquinoline
EI	Electron Impact ionization
Et	ethyl
Fmoc	9-fluorenylmethoxycarbonyl
g	gram(s)
GC	gas chromatography
h or hr	hour(s)
HATU	0-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	hexamethyldisilazane
HOAc	acetic acid
HOBt	hydroxybenzotriazole
HPLC	high pressure liquid chromatography
L	liter(s)
M	molar or molarity
m	multiplet
Me	methyl
mesyl	methanesulfonyl
mg	milligram(s)
MHz	megahertz (frequency)
Min	minute(s)
mL	milliliter(s)

Abbreviation	Meaning
mM	millimolar
mmol	millimole(s)
mol	mole(s)
MS	Mass spectral analysis
MTBE	methyl t-butyl ether
N	normal or normality
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
nM	nanomolar
NMO	N-methylmorpholine oxide
NMR	nuclear magnetic resonance spectroscopy
PEG	polyethylene glycol
pEY	poly-glutamine, tyrosine
Ph	phenyl
PhOH	phenol
PfP	pentafluorophenol
PfPy	pentafluoropyridine
PPTS	Pyridinium p-toluenesulfonate
Py	pyridine
PyBroP	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
q	quartet
RT	Room temperature
Sat'd	saturated
s	singlet
s-	secondary
t-	tertiary
t or tr	triplet
TBDMS	t-butyldimethylsilyl

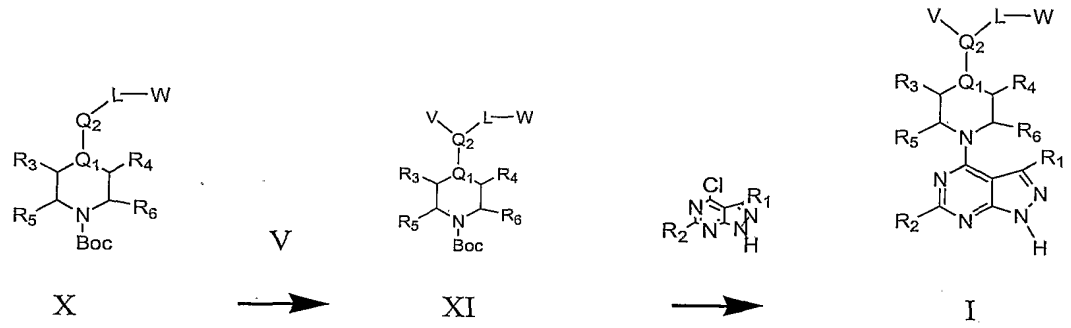
Abbreviation	Meaning
TES	triethylsilane
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMOF	trimethyl orthoformate
TMS	trimethylsilyl
tosyl	p-toluenesulfonyl
Trt	triphenylmethyl
μL	microliter(s)
μM	Micromole(s) or micromolar

Synthesis of Compounds

[0177] Scheme 1 depicts a general synthetic route for exemplary compounds of the invention according to Formula I, and are not intended to be limiting. Specific examples are described subsequently to this general synthetic description. With the description of the general route and the specific examples thereafter, one of ordinary skill in the art would be able to make compounds of the invention as described in the detailed description and claims.

[0178] Scheme 1 shows that in general, compounds according to Formula I can be made, for example, via a linear route, by reacting a compound of Formula X, having a Boc protecting group and an appropriate leaving group from Q_2, with a nucleophile of group V. The resulting compound is then dissolved in an appropriate solvent such as 1,4-dioxane, and the solution is reacted with Et_3N and 3-R_1-4-chloro-1R_2-pyrazolo[3,4-d]pyrimidine to arrive at a compound of Formula I. Formula I, R_1-R_6, Q_1, Q_2, L, V and W are as described above.

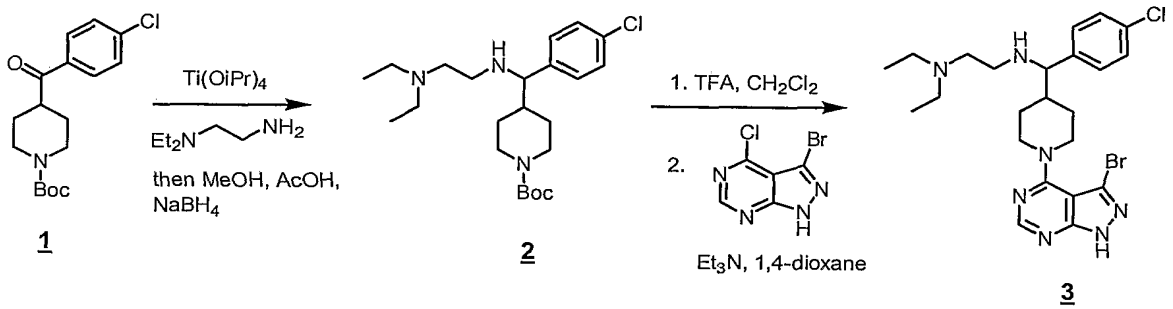
Scheme 1



[0179] One of ordinary skill in the art would also recognize that the description associated with Scheme 1 is a generalization, and that there are other combinations of steps and approaches that can be used to make compounds of the invention. The examples that follow provide much more detailed descriptions of making exemplary compounds of the invention.

[0180] The following examples serve to more fully describe the manner of using the above-described invention, as well as to set forth the best modes contemplated for carrying out various aspects of the invention. It is understood that these examples in no way serve to limit the true scope of this invention, but rather are presented for illustrative purposes. All references cited herein are incorporated by reference in their entirety. Generally, but not necessarily, each example set out below describes a multi-step synthesis as outlined above.

Example 1



N'-[[1-(3-Bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-piperidin-4-yl]-(4-chloro-phenyl)-methyl]-N,N-diethyl-ethane-1,2-diamine (3):

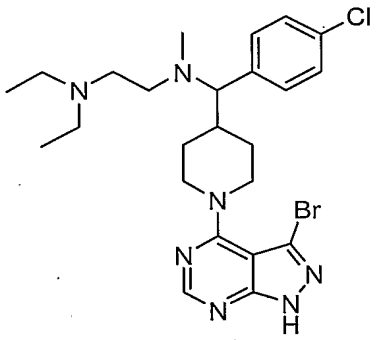
To a mixture of N-Boc-4-(4-chlorobenzoyl)piperidine (300 mg, 0.92 mmol) and 2-(diethylamino)ethylamine (215 mg, 1.85 mmol) at rt was added $Ti(O^iPr)_4$ (1.05 g, 3.70 mmol). The stirring was continued for 12 h. MeOH (3 mL) and AcOH (1 mL) were then added. Followed by careful addition of $NaBH_4$ (70 mg, 1.85 mmol) as small portions. The reaction mixture was then stirred for another 1 h and filtered through Celite. The Celite pad was washed with EtOAc. The EtOAc solution was washed with 5% NaOH, brine and dried over Na_2SO_4. Removal of the solvent gave the crude product (200 mg, 50%), which was used in the next step.

The crude product obtained above was treated with excess TFA in CH_2Cl_2 for 30 min. The mixture was concentrated, diluted with EtOAc, washed with 10% NaOH, dried over Na_2SO_4 and concentrated. The residue was dissolved in 1,4-dioxane (4 mL). To this solution was added Et_3N (0.33 mL, 2.35 mmol) and 3-Bromo-4-chloro-1H-pyrazolo[3,4-d]pyrimidine (87 mg, 0.37 mmol). The reaction mixture was heated to 70°C and the stirring was continued for 1 h.

Purification by preparation HPLC gave 3 (127 mg, 52%). The free-based product was converted to the HCl salt.

LC-MS (M+1): 522.5 (100%), 520.5 (80%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 14.07 (br s, 1 H), 10.81 (br s, 1 H), 10.05 (br s, 1 H), 8.30 (s, 1 H), 7.69 (d, J = 8.6 Hz, 2 H), 7.56 (d, J = 8.6 Hz, 2 H), 4.54-4.37 (m, 2 H), 3.60-3.40 (m, 5 H), 3.20-2.90



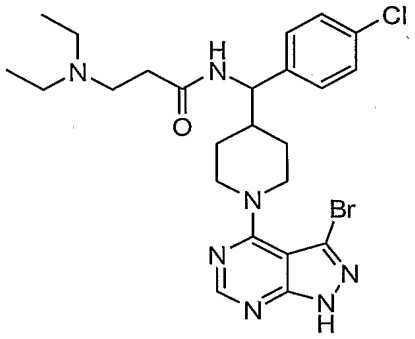
(m, 8 H), 2.24-2.21 (m, 1 H), 1.50-1.42 (m, 2 H), 1.24-1.15 (m, 6 H).

N'-[[1-(3-Bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-piperidin-4-yl]-(4-chloro-phenyl)-methyl]-N,N-diethyl-ethane-N"-methyl-1,2-diamine

LC-MS (M+1): 536.5 (100%), 534.5 (80%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 1 H), 7.41 (d, J = 8.3 Hz, 2 H), 7.25 (d, J = 8.3 Hz, 2 H), 4.50 (d, J = 13.2 Hz, 1 H), 4.34 (d, J = 12.8 Hz, 1 H), 3.36 (d, J = 10.4 Hz, 1 H), 3.20-3.00

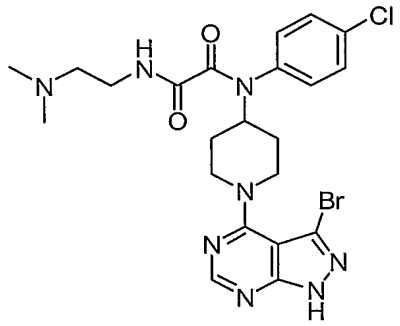
(m, 2 H), 2.50-2.40 (m, 2 H), 2.45 (q, J = 7.1 Hz, 4 H), 2.40-2.30 (m, 2 H), 2.25-2.20 (m, 1 H), 2.18-2.10 (m, 1 H), 2.05 (s, 3 H), 1.40-1.28 (m, 2 H), 1.18-1.08 (m, 1 H), 0.92 (t, J = 7.2 Hz, 6 H).



N-[[1-(3-Bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-piperidin-4-yl]-(4-chloro-phenyl)-methyl]-3-diethylamino-propionamide:

LC-MS (M+1): 550.4 (100%), 548.4 (80%).

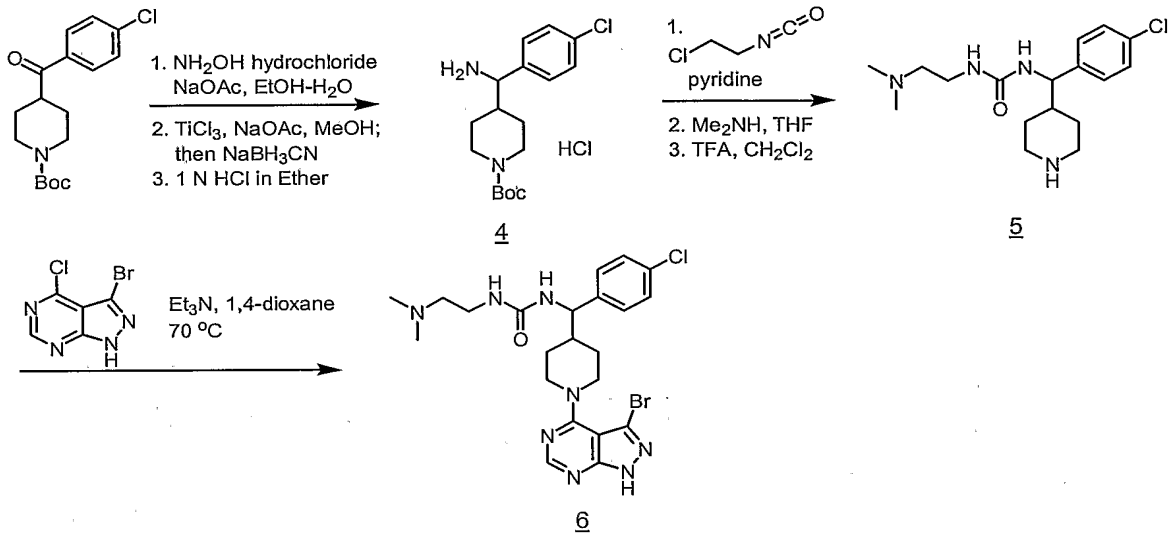
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (d, J = 9.0 Hz, 1 H), 8.28 (s, 1 H), 7.39 (d, J = 8.4 Hz, 2 H), 7.35 (d, J = 8.5 Hz, 2 H), 4.70 (t, J = 8.6 Hz, 1 H), 4.48 (d, J = 12.7 Hz, 1 H), 4.39 (d, J = 12.7 Hz, 1 H), 3.10-2.90 (m, 2 H), 2.70-2.50 (m, 2 H), 2.45-2.38 (m, 4 H), 2.30-2.10 (m, 2 H), 2.00-1.80 (m, 2 H), 1.40-1.30 (m, 3 H), 0.89 (t, J = 7.3 Hz, 6 H).



N-[1-(3-Bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-piperidin-4-yl]-N-(4-chloro-phenyl)-N'-(2-dimethylamino-ethyl)-oxalamide:

Observed M+, Bromine isotope: 549.1, 551.1 (1:1)

^{1}HNMR (*d6*-DMSO): 9.40 (br s, 1H), 8.90 (br t, 1H), 8.28 (s, 1H), 7.47 (d, 2H), 7.28 (d, 2h), 4.95 (m, 1H), 4.50 (d, 2H), 3.21 (m, 4H), 2.86 (d, 2H), 2.71 (d, 6H), 1.94 (d, 2H), 1.5 (m, 2H) ppm.



1-[[1-(3-Bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-piperidin-4-yl]-(4-chloro-phenyl)-methyl]-3-(2-dimethylamino-ethyl)-urea (6):

To a mixture of N-Boc-4-(4-chlorobenzoyl)piperidine (1.0 g, 3.08 mmol) in EtOH (25 mL) and H_2O (5 mL) was added hydroxylamine hydrochloride (536 mg, 7.72 mmol) and NaOAc (633 mg, 7.72 mmol). The reaction mixture was stirred under reflux for 3 h. EtOH was removed. The residue was dissolved in EtOAc, washed with brine, and dried over Na_2SO_4. Removal of EtOAc gave a mixture of the desired oximes (1.0 g, 96%).

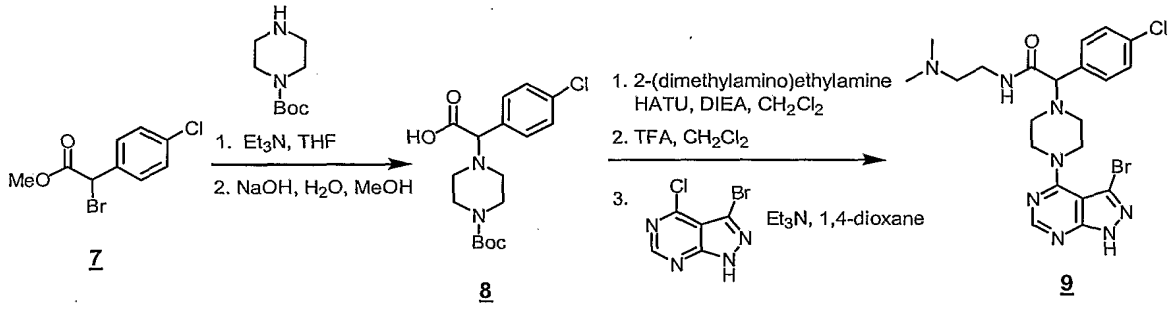
To a solution of aqueous $TiCl_3$ solution (4.8 g, 9.44 mmol, 30% in 2 N HCl) was added NaOAc (774 mg, 9.44 mmol) with stirring. The stirring was continued until a homogenous solution was achieved. The solution was then cooled to 0 °C, and the oximes (800 mg, 2.36 mmol) were added as a solution in MeOH (15 mL). The stirring was continued for another 1 h followed by the addition $NaBH_3CN$ (297 mg, 4.72 mmol). After stirred for additional 1 h, it was extracted with EtOAc. The EtOAc layer was washed with brine, and dried over Na_2SO_4. After filtration, the volume of EtOAc was reduced to about 40 mL. It was then treated with 4.7 mL of 1 N HCl/ether. The solid was filtered and washed with EtOAc. The desired primary amine HCl salt was dried at rt under vacuum.

To a solution of the primary amine hydrochloride (130 mg, 0.36 mmol) in pyridine (3 mL) was added 2-chloroethyl isocyanate (113 mg, 1.1 mmol). The solution was stirred at rt for 1 h. Pyridine was removed under reduced pressure. The residue was transferred to a pressure vessel containing 4 mL of 2 M Me_2NH/THF. The mixture was heated to 100 °C and stirred for 5 h. It was then cooled to rt and concentrated. The residue was treated with excess TFA in CH_2Cl_2. The crude product was free-based and was used in the next reaction.

The crude product (about 0.34 mmol) was then reacted with 3-Bromo-4-chloro-1H-pyrazolo[3,4-d]pyrimidine (55 mg, 0.23 mmol) in the presence of Et_3N (172 mg, 1.7 mmol) in 1,4-dioxane (2 mL) at 70 °C for 1 h. The reaction mixture was then diluted with EtOAc. The organic phase was washed with sat. aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. The residue was triturated with ether and further purified by column chromatography (CH_2Cl_2 : MeOH = 100 : 10).

LC-MS (M+1): 537.5 (100%), 535.4 (80%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 1 H), 7.36 (d, J = 8.6 Hz, 2 H), 7.24 (d, J = 8.5 Hz, 2 H), 6.75 (d, J = 8.7 Hz, 1 H), 5.83 (t, J = 5.3 Hz, 1 H), 4.55-4.47 (m, 3 H), 3.20-2.80 (m, 5 H), 2.20 (t, J = 6.1 Hz, 2 H), 2.09 (s, 6 H), 1.80-1.70 (m, 1 H), 1.48-1.30 (m, 3 H).



2-[4-(3-Bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-piperazin-1-yl]-2-(4-chloro-phenyl)-N-(2-dimethylamino-ethyl)-acetamide (9):

2-Bromo-(p-chlorophenyl)-acetic acid methyl ester was prepared from (4-chlorophenyl)-acetic acid methyl ester (2.5 g, 13.5 mmol) and NBS (2.52 g, 14.1 mmol) in CCl_4.

To a solution of 2-Bromo-(p-chlorophenyl)-acetic acid methyl ester (1.0 g, 3.79 mmol) and Et_3N (1.6 mL, 12 mmol) in THF (10 mL) was added N-Boc piperazine (705 mg, 3.79 mg).

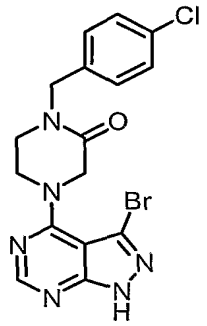
The mixture was stirred at rt until the bromoester was consumed. The reaction progress was monitored by ^{1}H NMR. The reaction mixture diluted with EtOAc, washed with 5% NaOH, brine and dried over Na_2SO_4. Removal of the solvents gave the crude product.

The crude product (414 mg) obtained above was dissolved in 1:1 MeOH-H_2O (4 mL). NaOH (90 mg, 2.25 mmol) was added. The mixture was stirred for 2 h at rt and was concentrated. The residue was dissolved in H_2O (5 mL) and washed with ether (2 x 5 mL). To the aqueous phase was added AcOH until PH = 8. It was then extracted with EtOAc. The organic phases were combined, washed with brine, and dried over Na_2SO_4. Removal of EtOAc gave the crude carboxylic acid, which was used in the next step.

To a solution of the crude carboxylic acid (76 mg, 0.21 mmol) and 2-(dimethylamio)ethylamine (75 mg, 0.85 mmol) in CH_2Cl_2 (4 mL) was added DIEA (110 mg, 0.85 mmol) and HATU (155 mg, 0.41 mmol). The mixture was stirred at rt for 2 h and diluted with EtOAc. The organic phase was washed with 5% NaOH, brine and dried over Na_2SO_4. Upon removal of solvents, the residue was treated with excess TFA in CH_2Cl_2. The crude product was then reacted with 3-Bromo-4-chloro-1H-pyrazolo[3,4-d]pyrimidine (30 mg, 0.14 mmol) in the presence of Et_3N (101 mg, 1.0 mmol) in 1,4-dioxane (2 mL) at 70° C for 1 h. The mixture was then concentrated. Purification by preparation HPLC gave 6 (25 mg, 34%).

LC-MS (M+1): 523.4 (100%), 521.4 (80%).

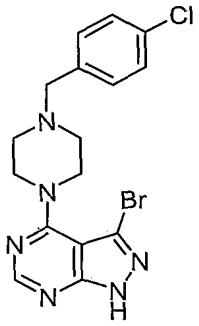
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (s, 1 H), 8.17 (t, J = 5.7 Hz, 1 H), 7.45-7.40 (m, 4 H), 3.95 (s, 1 H), 3.81 (br s, 4 H), 3.16 (q, J = 5.9 Hz, 2 H), 2.60-2.52 (m, 2 H), 2.50-2.44 (m, 2 H), 2.28 (t, J = 6.6 Hz, 2 H), 2.14 (s, 6 H).



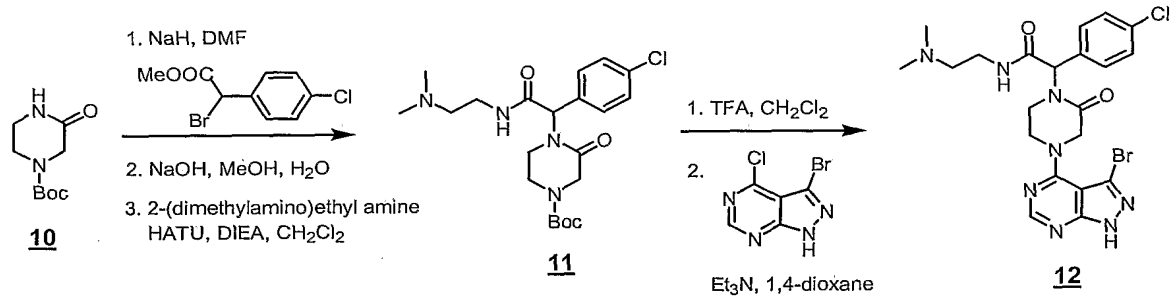
4-(3-Bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-1-(4-chloro-benzyl)-piperazin-2-one:

LC-MS (M+1): 423.3 (100%), 421.3 (80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.20 (br s, 1 H), 8.45 (s, 1 H), 7.32 (d, J = 8.6 Hz, 2 H), 7.24 (d, J = 8.4 Hz, 2 H), 4.66 (s, 2 H), 4.63 (s, 2 H), 4.17 (t, J = 5.5 Hz, 2 H), 3.50 (t, J = 5.4 Hz, 2 H).



3-Bromo-4-[4-(4-chloro-benzyl)-piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine:
Observed M+, Bromine isotope: 406.9, 408.9 (1:1)
^{1}HNMR (*d6*-DMSO): 10.00 (br s, 1H), 8.42 (s, 1H), 7.54 (q, 4H), 4.40 (m, 4H), 4.41 (s, 2H), 3.46-3.20 (m, 4H) ppm.

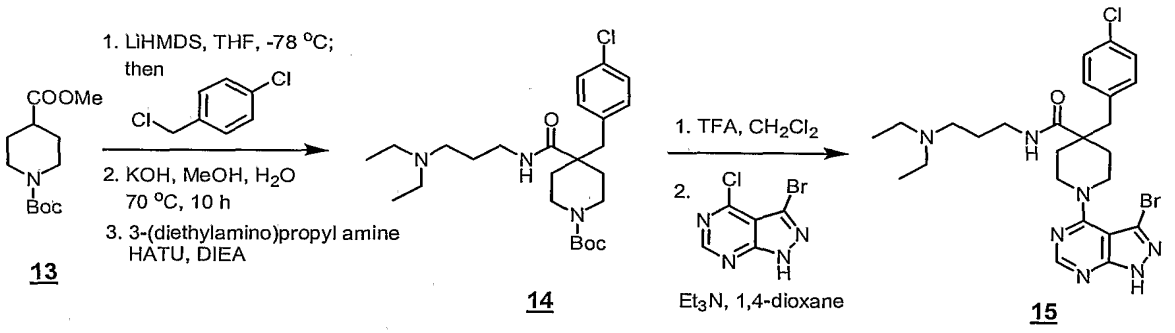


2-[4-(3-Bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-2-oxo-piperazin-1-yl]-2-(4-chloro-phenyl)-N-(2-dimethylamino-ethyl)-acetamide (12):
To a solution of 4-Boc piperazinone (240 mg, 1.2 mmol) in DMF (3 mL) was added NaH (58 mg, 1.44 mmol, 60% in mineral oil). The resulting solution was stirred for 30 min at rt. 2-Bromo-(p-chlorophenyl)-acetic acid methyl ester (315 mg, 1.2 mmol) was then added. The reaction mixture was stirred for additional 3 h at rt. It was diluted with EtOAc, and washed with brine, dried over Na_2SO_4. Removal of EtOAc gave the desired product, which was then treated with NaOH (102 mg, 2.56 mmol) in MeOH (2 mL) and H_2O (1 mL) for 3 h. MeOH was removed under reduced pressure. The residue was dissolved in H_2O (5 mL), and washed

with ether. The aqueous phase was acidified with 1 N HCl. The solid was filtered, washed with H_2O, and dried under vacuum. The crude carboxylic acid (165 mg, 0.44 mmol) was mixed with 2-(dimethylamio)ethylamine (157 mg, 1.79 mmol), HATU (680 mg, 1.79 mmol), and DIEA (231 mg, 1.79 mmol) in DCM (2 mL). The stirring was continued for 2h. The mixture was concentrated and the residue was dissolved in EtOAc. The organic phase was washed with sat. $NaHCO_3$ and brine. Removal of solvent gave the crude coupling product. The crude product obtained above was treated with excess TFA in DCM for 30 min. Upon removal of excess TFA and DCM, the residue (about 0.4 mmol) was free-based and then reacted with 3-Bromo-4-chloro-1H-pyrazolo[3,4-d]pyrimidine (25 mg, 0.11 mmol) in the presence of Et_3N (126 mg, 2.5 mmol) in 1,4-dioxane (2 mL) at 70 °C for 1 h. The mixture was concentrated. The crude product was purified by preparation HPLC.

LC-MS (M+1): 537.4 (100%), 535.4 (80%).

^1H NMR (400 MHz, DMSO-d_6) δ 8.33-8.31 (m, 2 H), 7.45 (d, J = 8.4 Hz, 2 H), 7.31 (d, J = 8.5 Hz, 2 H), 6.21 (s, 1 H), 4.55-4.42 (m, 2 H), 4.05-4.00 (m, 3 H), 3.74-3.68 (m, 1 H), 3.32-3.22 (m, 1 H), 3.20-3.10 (m, 1 H), 3.08-3.00 (m, 1 H), 2.28 (t, J = 6.5 Hz, 2 H), 2.13 (s, 6 H).



1-(3-Bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-4-(4-chloro-benzyl)-piperidine-4-carboxylic acid (3-diethylamino-propyl)-amide (15):

To a –78 °C solution of 1-N-Boc-4-piperidinecarboxylic acid methyl ester (2.0 g, 8.22 mmol) in THF (30 mL) was added LiHMDS (1.0 M in THF, 12 mL, 12.3 mmol) dropwise. The stirring was continued for 45 min. Then 4-chlorobenzyl chloride (1.59 g, 9.86) was added as a solution in THF (3 mL). The mixture was stirred for 5 h while it was warmed slowly to rt. H_2O was added to quench the reaction. It was then extracted with EtOAc. The organic phase was washed with brine, and dried over Na_2SO_4. Removal of EtOAc gave the crude product.

The crude methyl ester (1.0 g, 2.72 mmol) was mixed with KOH (440 mg, 10.8 mmol) in MeOH (5 mL) and H_2O (5 mL). The mixture was stirred for 10 h at 80 °C. MeOH was removed; the residue was diluted with 20 mL of H_2O. The aqueous solution was washed with ether and acidified with 4 N HCl. The product was extracted with EtOAc, washed with brine, and dried over Na_2SO_4. Removal of EtOAc gave desired carboxylic acid with above 90% purity. The carboxylic acid (250 mg, 0.71 mmol) was mixed with 2-(dimethylamio)propylamine (275 mg, 2.11 mmol), HATU (535 mg, 1.41 mmol), and DIEA (361 mg, 2.8 mmol) in DCM (6 mL). The stirring was continued for 2h. CH_2Cl_2 was removed and the residue was dissolved in EtOAc. The organic phase was washed with sat. $NaHCO_3$ and brine. Removal of solvent gave the crude product.

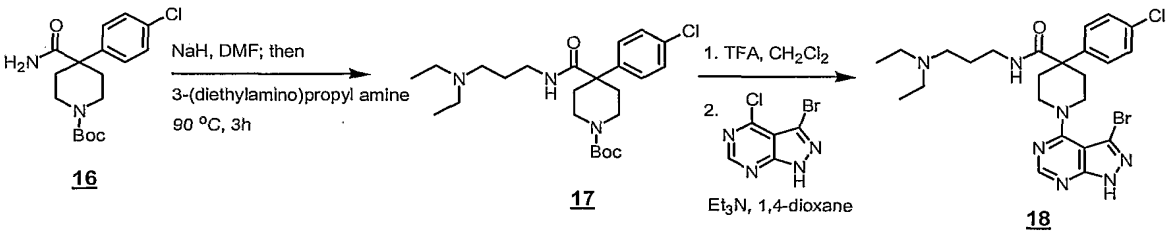
The crude product (about 0.7 mmol) obtained above was treated with excess TFA in DCM for 30 min. Upon removal of excess TFA and DCM, the residue was free-based and then reacted with 3-Bromo-4-chloro-1H-pyrazolo[3,4-d]pyrimidine (98 mg, 0.42 mmol) in the presence of Et_3N (354 mg, 3.5 mmol) in 1,4-dioxane (2 mL) at 70 °C for

1 h. The mixture was concentrated. The crude product was purified by preparation HPLC.

HCL salt:

LC-MS (M+1): 564.4 (100%), 562.4 (80%).

^1H NMR (400 MHz, DMSO-d_6) δ 14.17 (br s, 1 H), 10.34 (br s, 1 H), 8.33 (s, 1 H), 8.11 (br s, 1 H), 7.34 (d, J = 7.9 Hz, 2 H), 7.10 (d, J = 7.7 Hz, 2 H), 4.27 (br d, J = 13.4 Hz, 2 H), 3.28-3.27 (m, 2 H), 3.20-3.10 (m, 2 H), 3.10-3.00 (m, 4 H), 3.00-2.90 (m, 2 H), 2.85 (s, 2 H), 2.17 (br d, J = 13.0 Hz, 2 H), 1.82 (br s, 2 H), 1.64 (br s, 2 H), 1.21-1.18 (m, 6 H).



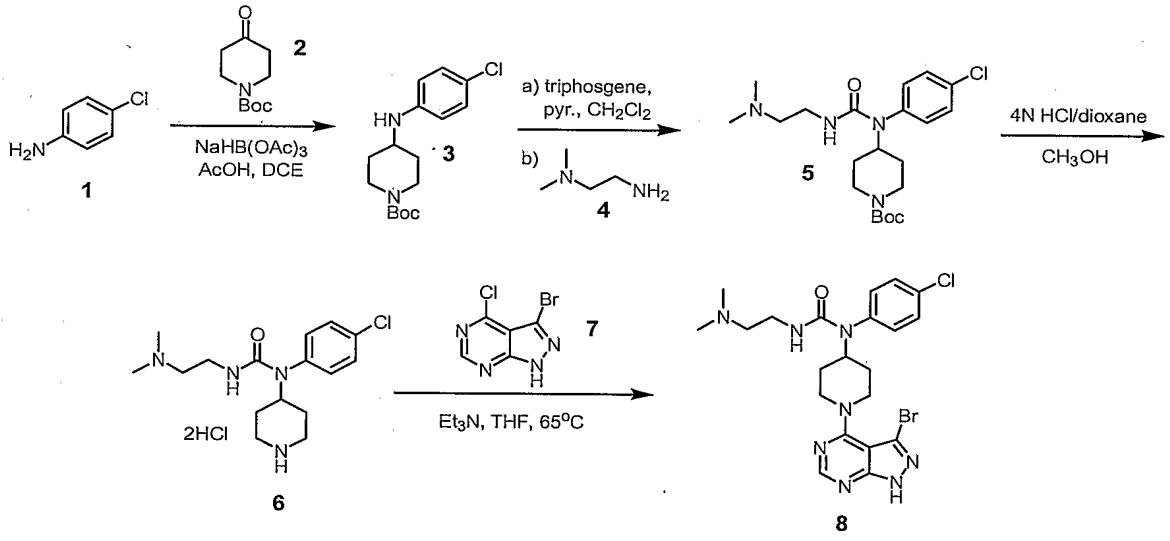
1-(3-Bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-4-(4-chloro-phenyl)-piperidine-4-carboxylic acid (3-diethylamino-propyl)-amide (18):

To a solution of N-Boc-4-(p-chlorophenyl)-piperidine-4-carbamide (135 mg, 0.40 mmol) in DMF (4 mL) was added NaH (60% in mineral oil, 20 mg, 0.5 mmol). The stirring was continued for 30 min. Then 3-(diethylamino)propyl chloride (90 mg, 0.60) was added. The mixture was then warmed to 90 °C. The stirring was continued for another 3 h. To the cooled mixture was added H_2O. It was then extracted with EtOAc. The organic phase was washed with brine, and dried over Na_2SO_4. Removal of EtOAc gave the crude product.

The crude product (about 0.4 mmol) obtained above was treated with excess TFA in DCM for 30 min. Upon removal of excess TFA and DCM, the residue was free-based and then reacted with 3-Bromo-4-chloro-1H-pyrazolo[3,4-d]pyrimidine (40 mg, 0.17 mmol) in the presence of Et_3N (152 mg, 1.5 mmol) in 1,4-dioxane (2 mL) at 70 °C for 1 h. The mixture was concentrated. The crude product was purified by preparation HPLC.

LC-MS (M+1): 550.4 (100%), 548.4 (80%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (s, 1 H), 7.83 (t, J = 5.5 Hz, 1 H), 7.41 (s, 4 H), 4.25 (br d, J = 13.4 Hz, 2 H), 3.37 (br t, J = 11.9 Hz, 2 H), 3.08 (q, J = 6.4 Hz, 2 H), 2.63 (br d, J = 13.7 Hz, 2 H), 2.34 (q, J = 7.2 Hz, 4 H), 2.23-2.19 (m, 2 H), 1.99-1.92 (m, 2 H), 1.49-1.41 (m, 2 H), 0.85 (t, J = 7.2 Hz, 6 H).



Piperido-chloroaniline (3). To a 200 mL recovery flask were added 4-chloroaniline 1 (2.00 g, 15.7 mmol, 1.0 eq.), 1-Boc-4-piperidone 2 (3.44 g, 17.2 mmol, 1.1 eq.), 1,2-dichloroethane (35 mL), and acetic acid (3 mL). The mixture was stirred at room temperature for 20 min.,

whereupon $NaBH(OAc)_3$ (5.00 g, 23.5 mmol, 1.5 eq.) was added in three portions over a period of 10 min. The reaction mixture was stirred at room temperature for three hours. TLC analysis showed complete consumption of starting material. The reaction mixture was concentrated and then diluted with EtOAc (200 mL). The organic layer was washed with H_2O (2 x 50 mL) and brine (1 x 50 mL). The combined aqueous layers were extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to give yellowish oil. Flash chromatography (100% CH_2Cl_2 to 5% CH_3OH/CH_2Cl_2) yields a colorless oil which later solidifies to an off-white solid (2.87 g, 59%).

Urea (5). To a 100 mL recovery flask were added aniline 3 (1.00 g, 3.22 mmol, 1.0 eq.), dichloromethane (45 mL), and pyridine (274 μL, 3.38 mmol, 1.05 eq.). Triphosgene (574 mg, 1.93 mmol, 0.6 eq.) was added and the reaction mixture, which turned light-yellowish in color, was stirred at room temperature. TLC analysis at 45 minutes indicated that the starting material had been consumed. Unsym-dimethylethylenediamine 4 (1.78 mL, 16.1 mmol, 5.0 eq.) was added, whereupon the reaction mixture became cloudy. After stirring for several minutes, the reaction mixture became homogeneous. After reaction time of 2.5 h, TLC analysis revealed a lower Rf spot. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and $NaHCO_3$ (sat'd aq., 100 mL). The organic layer was washed with brine (50 mL). The combined aqueous layers were extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to give yellowish oil which solidified overnight to give an off-white solid which was used in subsequent reactions without further purification. (1.40 g, 100%).

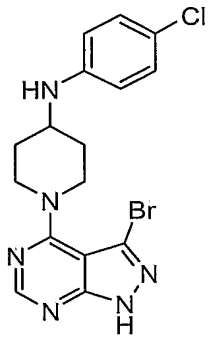
Piperidine dihydrochloride (6). To a 25 mL recovery flask was added urea 5 (250 mg, 0.588 mmol, 1.0 eq.) and CH_3OH (5 mL). 4N HCl/dioxane (7 mL) was added and the reaction mixture was stirred for 2h at room temperature. The reaction mixture was concentrated to give a bronze film that was used in the next reaction without further purification.

Bromopyrazolopyrimidine (8) To a 25 mL recovery flask were added 6 (230 mg, 0.708 mmol, 1.05 eq.), THF (10 mL), Et_3N (470 μL, 3.37 mmol, 5.0 eq.), and chloropyrazolopyrimidine 7

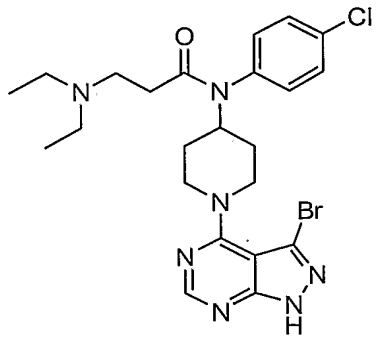
(157 mg, 0.674 mmol, 1.0 eq.). The reaction mixture was stirred at reflux for 1.5h. The reaction was concentrated and diluted with EtOAc (50 mL) and $NaHCO_3$ (sat'd aq., 50 mL). The organic layer was washed with H_2O (50 mL) and brine (50 mL). The combined aqueous layers were extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to give a light-brown oil that slowly solidified to a white solid (308 mg crude). The crude material was purified via flash chromatography (10% to 20% CH_3OH/CH_2Cl_2) to give a colorless oil (205 mg, 58%).

Observed M+H: 523.1 (Br isotope)

NMR, DMSO-d6, HCl salt : δ10.40 (s, 1H), 8.30 (s, 1H), 7.49 (d, 2H), 7.26 (d, 2H), 4.88 (s, 1H), 4.59 (m, 2H), 4.50 (obs m, 2H), 3.34-3.23 (m, 4H), 3.07-3.03 (m, 2H), 2.73 (s, 6H), 1.94 (d, 2H), 1.38-1.34 (m, 2H) ppm.



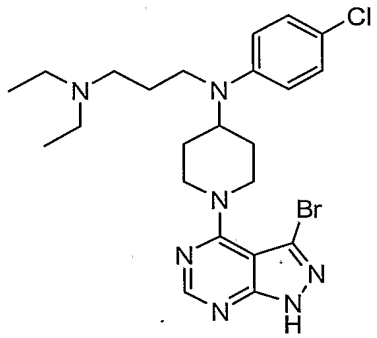
[1-(3-Bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-piperidin-4-yl]-(4-chloro-phenyl)-amine:
Obs. MS 408.9 (M+H),
(DMSO-d_6) δ 8.32 (s, 1H), 7.12 (d, 2H), 6.71 (d, 2H), 4.40 (d, 2H), 3.62 (s, 1H), 3.35 (t, 2H), 2.08 (d, 2H), 1.55 (m, 2H) ppm.



N-[1-(3-Bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-piperidin-4-yl]-N-(4-chloro-phenyl)-3-diethylamino-propionamide:

Obs. MS 536.1 (M+H),

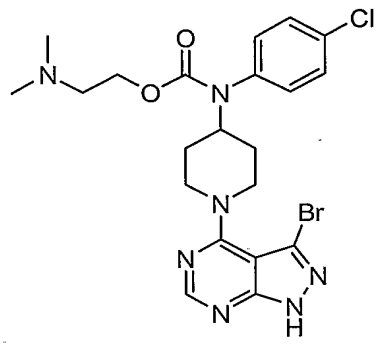
(DMSO-d_6) δ 9.59 (br. s, 1H), 8.28 (s, 1H), 7.58 (d, 2H), 7.37 (d, 2H), 4.80 (m, 1H), 4.50 (d, 2H), 3.21 (m, 4H), 3.0 (m, 4H), 2.34 (m, 2H), 1.92 (d, 2H), 1.39 (m, 2H), 1.17 (t, 6H) ppm.



N-[1-(3-Bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-piperidin-4-yl]-N-(4-chloro-phenyl)-N'-di-ethyl-propane-1,3-diamine

Obs. MS 522.1 (M+H),

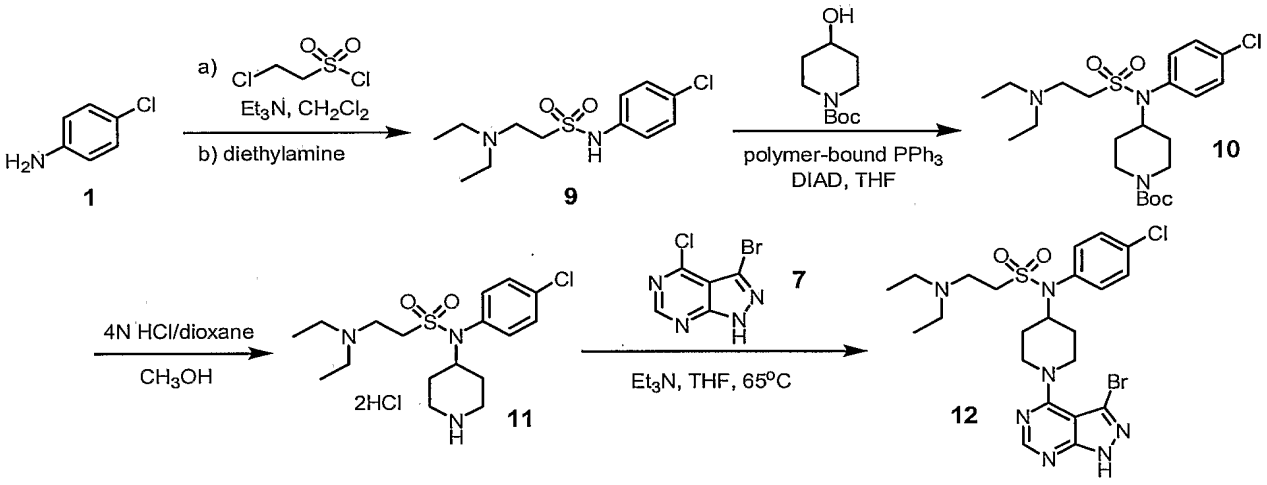
(CD_3OD) δ 8.27 (s, 1H), 7.18 (d, 2H), 6.90 (d, 2H), 4.90 (m, 2H), 4.71 (d, 2H), 3.91 (m, 1H), 3.28 (m, 4H), 2.62 (m, 4H), 1.93 (m, 4H), 1.70 (m, 2H), 1.08 (t, 6H) ppm.



[1-(3-Bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-piperidin-4-yl]-(4-chloro-phenyl)-carbamic acid 2-dimethylamino-ethyl ester:

Observed M+H: 524.1

NMR, DMSO-d6, HCl salt: δ 10.66 (br s, 1H), 8.29 (s, 1H), 7.46 (d, 2H), 7.29 (d, 2H), 4.51-4.48 (m, 3H), 4.34 (m, 2H), 3.29-3.23 (m, 4H), 2.67-2.45 (obs s, 6H), 2.01 (d, 2H), 1.47-1.41 (m, 2H) ppm.



Sulfonamide (9). To a 250 mL round-bottomed flask were added in order 4-chloroaniline (2.00 g, 15.7 mmol, 1.0 eq.), dichloromethane (100 mL), triethylamine (6.55 mL, 47.0 mmol, 3.0 eq.), and 2-chloro-1-ethane sulfonyl chloride (2 mL, 18.8 mmol, 1.2 eq.). While stirring at room temperature for 2h the reaction became cloudy. Diethylamine (8.14 mL, 78.3 mmol, 5.0 eq.) was added and the reaction immediately became clear and homogeneous. After stirring for 2h, TLC analysis (10% CH_3OH/CH_2Cl_2) indicated consumption of starting material. The reaction mixture was quenched with H_2O (50 mL). The organic layer was washed with additional H_2O (50 mL) and brine (50 mL). The aqueous layers were extracted with CH_2Cl_2 (2

x 50 mL). The organic layers were combined and dried over anhydrous Na_2SO_4, filtered, and concentrated to give a bronze oil (5 g crude). Column chromatography (2% to 5% CH_3OH/CH_2Cl_2) yields 9 as a light-bronze oil (3.15 g, 69%).

Piperidyl-sulfonamide (10). Toa 100 mL recovery flask were added polymer-bound PPh_3 (3 mmol/g loading, 841 mg, 2.52 mmol, 1.5 eq.), THF (30 mL), and diisopropylazodicarboxylate (434 μL, 2.19 mmol, 1.3 eq.). The flask was shaken for 5 min. 4-hydroxy-1-Boc-piperidine (440 mg, 2.19 mmol, 1.3 eq.) was added and the flask was shaken for an additional 5 min. A solution of sulfonamide 9 (488 mg, 1.68 mmol, 1.0 eq.) in THF (10 mL) was prepared and added to the reaction mixture. The reaction mixture was stirred at room temperature for 1h, upon which LC/MS analysis showed formation of product, but with a large amount of starting material present. Additional DIAD (134 μL, 0.673 mmol, 0.4 eq.) and alcohol (135 mg, 0.673 mmol, 0.4 eq.) was added and the reaction mixture was heated at 50°C overnight. The reaction mixture was filtered through a Celite pad and concentrated to give a yellow oil (1.86 g crude). Column chromatography (2% to 8% CH_3OH/CH_2Cl_2) yields **10** as a light-yellow oil (597 mg, 75%).

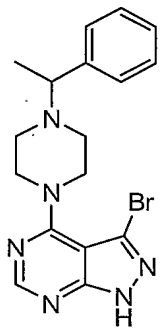
Piperidine dihydrochloride (11). To a 100 mL recovery flask was added 10 (597 mg, 1.26 mmol, 1.0 eq.) and CH_3OH (15 mL). 4N HCl/dioxane (10 mL) was added and the reaction mixture was stirred for 2h at room temperature. The reaction mixture was concentrated to give a bronze film that was used in the next reaction without further purification.

Bromopyrazolopyrimidine (12) To a 25 mL recovery flask were added 11 (563 mg, 1.26 mmol, 2.0 eq.), *i*-PrOH (10 mL), Et_3N (660 μL, 3.78 mmol, 6.0 eq.), and chloropyrazolopyrimidine 7 (147 mg, 0.630 mmol, 1.0 eq.). The reaction mixture was stirred at reflux for 1.5h. The reaction was concentrated and diluted with EtOAc (50 mL) and $NaHCO_3$ (sat'd aq., 50 mL). The organic layer was washed with H_2O (50 mL) and brine (50 mL). The combined aqueous layers were extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to give a light-brown solid that was purified via reverse-phase, preparative HPLC. The fractions containing desired product were collected, neutralized with $NaHCO_3$ (sat'd aq.), and extracted with

EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to give an off-white solid (54 mg, 7.5%).

Observed M+H: 572.1

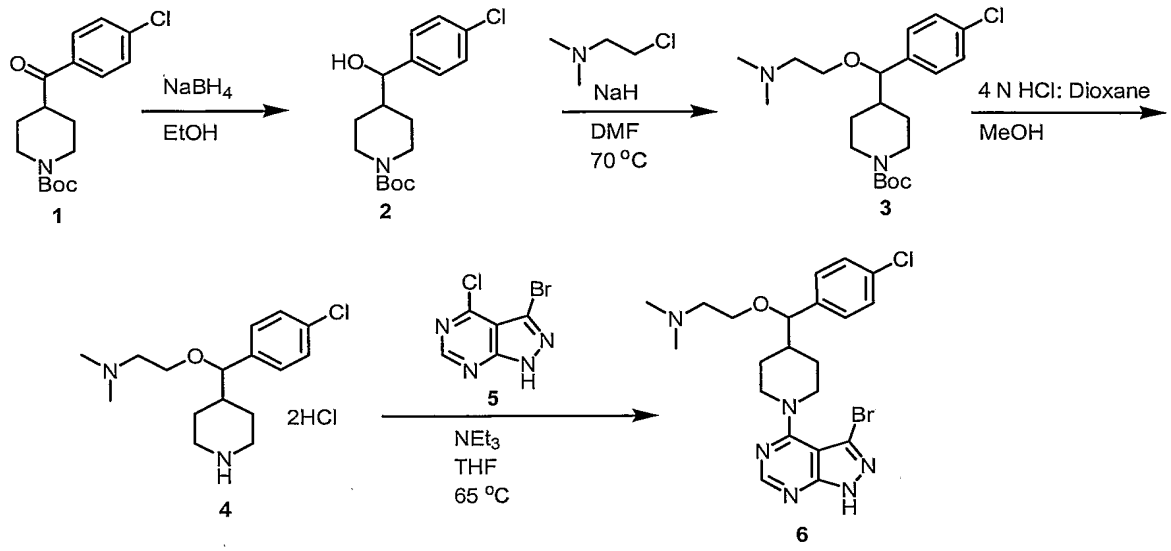
NMR, DMSO-d6, HCl salt: δ 10.51 (br s, 1H), 8.89 (s, 1H), 7.52 (d, 2H), 7.39 (d, 2H), 4.78-4.75 (m, 2H), 4.50 (d, 2H), 4.33 (m, 1H), 3.86 (m, 2H), 3.41 (m, 2H), 3.26-3.18 (m, 6H), 2.12 (d, 2H), 1.42 (m, 2H), 1.24-1.14 (m, 6H) ppm.



3-Bromo-4-[4-(1-phenyl-ethyl)-piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine:

Obs. MS 387.0 (M+H),

(DMSO-d_6) δ 10.18 (br. s, 1H), 8.43 (s, 1H), 7.52 (m, 5H), 4.60 (m, 2H), 4.49 (m, 1H), 3.90 (m, 2H), 3.20, (m, 2H), 3.05 (m, 2H), 2.70 (d, 3H) ppm.



Benzyl alcohol (2). To a round bottom flask, 1.24 g (3.84 mmol) of ketone 1 was dissolved in 40 mL of ethanol. To this solution, 145 mg (3.84 mmol) of $NaBH_4$ was added and stirred at room temperature for 2 h. The crude reaction was concentrated in vacuum. Ethyl acetate and water were added, and the organic layer was washed with H_2O (2x) and brine. The organic layer was dried with Na_2SO_4, filtered and concentrated to afford 1.25 g (3.84 mmol) of the alcohol 2.

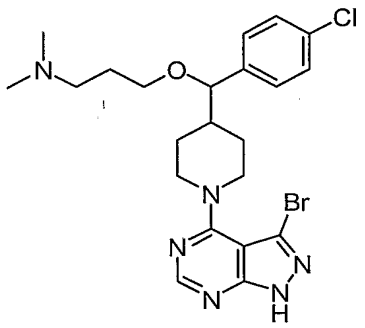
Dimethylaminoethyl ether (3). To a round bottom flask, 300 mg (0.923 mmol) of 2 was dissolved in 12 mL of DMF. To this solution, 92 mg (2.30) of NaH (60% dispersion in mineral oil) was added and stirred for 10 minutes followed by addition of 146 mg (1.01 mmol) of (2-chloro-ethyl)-dimethyl-amine hydrogen chloride. This reaction mixture was stirred at 70 °C for 12 hours and allowed to cool to room temperature. Ethyl acetate and 10% LiCl were added. The organic layer was washed with this LiCl solution three times, distilled water and brine. The organic layer was dried with Na_2SO_4, filtered and concentrated to afford 380 mg of crude product 3, which was taken on without further purification.

Dimethylaminoethyl ether dihydrochloride (4). To a round bottom flask, 380 mg (0.957 mmol) of 3 was dissolved in 3 mL of methanol. To this solution 3 mL of 4 N HCl in dioxane was added slowly, stirred at room temperature for 1 h and concentrated to afford a quantitative amount (354 mg) of 4.

Bromopyrazolopyrimidine (6). To a round bottom flask, 354 mg (0.957 mmol) of 4, 10 mL of THF and 0.8 mL (5.74 mmol) of NEt_3 were added. To this suspension, 223.4 mg (0.957 mmol) of 5 was added and stirred at 65 °C for 30 minutes. The crude reaction was concentrated. Ethyl acetate and distilled water were added and the organic layer was washed with water twice and brine once. The organic layer was dried with Na_2SO_4, filtered, and concentrated. The crude material was purified by preparative HPLC to afford 50.5 mg of 6 (0.102 mmol, 10.7 %).

Observed M+H: 495.0

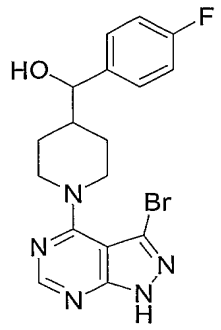
NMR, DMSO-d6, HCl salt: δ 8.30 (s, 1H), 7.50 (d, 2H), 7.39 (d, 2H), 4.45 (m, 2H), 4.20 (d, 1H), 3.71 (m, 2H), 3.43 (m, 1H), 3.23 (m, 2H), 3.03 (m, 2H), 2.80 (d, 3H), 2.75 (d, 3H), 2.13-1.90 (m, 2H), 1.51-1.23 (m, 2H) ppm.



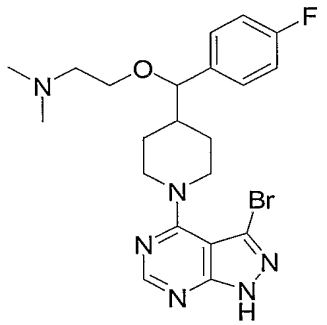
{3-[[1-(3-Bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-piperidin-4-yl]-(4-chloro-phenyl)-methoxy]-propyl}-dimethyl-amine

Obs. MS 509.0 (M+H),

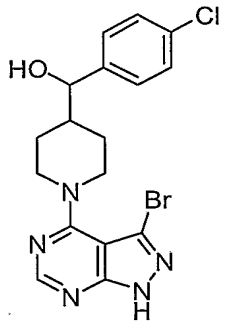
(DMSO-d6) δ 8.30 (s, 1H), 7.46 (d, 2H), 7.32 (d, 2H), 4.41 (dd, 2H), 4.11 (d, 1H), 3.22 (m, 2H), 3.06 (m, 4H), 2.72 (s, 6H), 2.08 (d, 1H), 1.88 (m, 2H), 1.51-1.32 (m, 4H) ppm.



[1-(3-Bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-piperidin-4-yl]-(4-fluoro-phenyl)-methanol:
Observed M+H, Bromine isotope: 406.1,408.1 (1:1)
^{1}HNMR (*d6*-DMSO): δ 8.21 (s, 1H), 7.42 (d, 2H), 7.20 (d, 2H), 4.45 (m, 3H), 2.98 (q, 2H), 1.90 (d, 1H), 1.80 (br s, 1H), 1.40 (m, 4H) ppm.

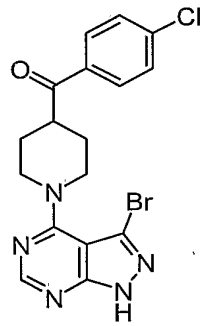


{2-[[1-(3-Bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-piperidin-4-yl]-(4-fluoro-phenyl)-methoxy]-ethyl}-dimethyl-amine:
Observed M+H, Bromine isotope: 477.1,479.1 (1:1)
^{1}HNMR (*d6*-DMSO): δ10.25 (br s, 1H), 8.25 (s, 1H), 7.42 (t, 2H), 7.20 (t, 2H), 4.80 (m, 1H), 4.20 (d, 1H), 3.45 (m, 2H), 3.20 (m, 4H), 2.70 (d, 6H), 2.10 (d, 1H), 2.00 (m, 1H), 1.40 (m, 4H) ppm.



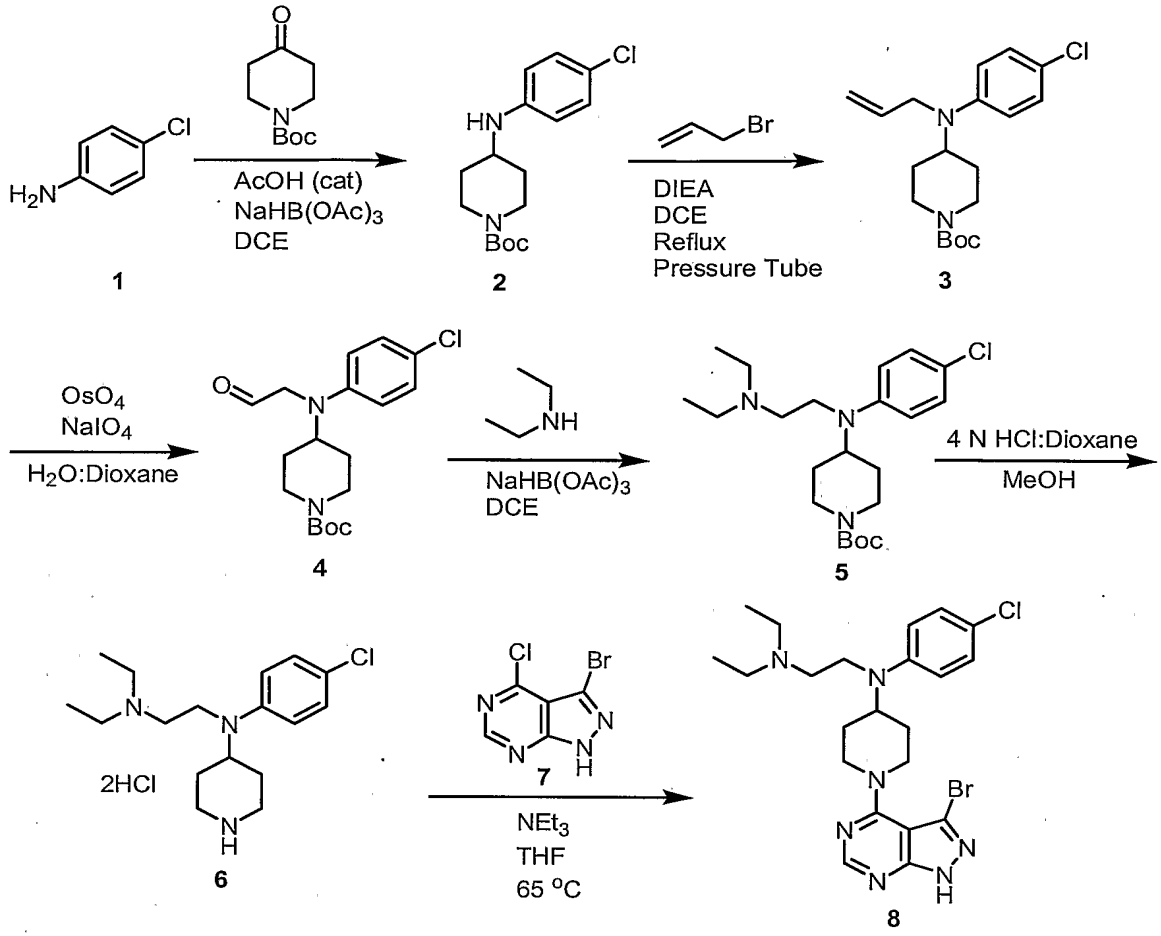
[1-(3-Bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-piperidin-4-yl]-(4-chloro-phenyl)-methanol: Observed M+, Bromine isotope: 421.9, 423.9 (1:1)

^{1}HNMR (*d6*-DMSO): δ 8.27 (s, 1H), 7.36 (m, 4H), 5.40 (d, 1H), 4.45 (m, 1H), 4.33(t,1H), 2.99 (m, 2H), 1.87 (m, 2H), 1.41 (m, 4H) ppm.



[1-(3-Bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-piperidin-4-yl]-(4-chloro-phenyl)-methanone: Observed M+, Bromine isotope: 420.4, 422.4 (1:1)

^{1}HNMR (*d6*-DMSO): δ 8.30 (s, 1H), 8.04 (d, 2H), 7.61 (d, 2H), 4.46 (d, 2H), 3.82 (m, 1H), 3.32 (m,2H), 1.95 (d, 2H), 1.73 (dq, 2H) ppm.



Allylamine (3). To a round bottom flask 500 mg (1.61 mmol) of 2 was dissolved in 10 mL of dichloroethane. To this solution, 1.12 mL (6.44 mmol) of DIEA and 1.4 mL (16.1 mmol) of allyl bromide were added. The reaction mixture was stirred at 85 °C for 12 h and allowed to cool to room temperature. Ethyl acetate and distilled water were added and the organic layer was washed with water twice and brine once, then dried with Na_2SO_4, filtered and concentrated to give the crude product. The product was further purified over silica using hexane: ethyl acetate (20:1) to afford 504 mg of final alkene product 3 (89%).

Aldehyde (4). To a round bottom flask 213.5 mg (0.608 mmol) of 3, followed by the addition 8 mL of a 1:1 mixture of water and dioxane. To this suspension a catalytic amount of OsO_4 was added and stirred at room temperature for 10 minute followed by an addition of 260.3 mg of $NaIO_4$. The reaction mixture was stirred for 12 h. Ethyl acetate and distilled water were

added and the organic layer was washed with water twice and brine once, then dried with Na_2SO_4, filtered and concentrated to give the crude product. The product was further purified over silica using hexane: ethyl acetate (7:3) to afford 60 mg of final aldehyde product 4 (28%).

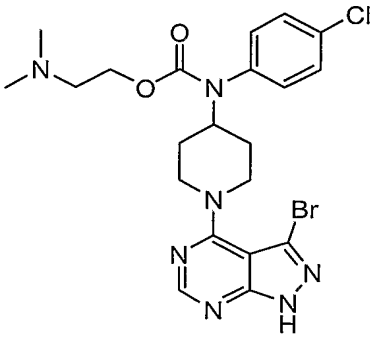
Diethylaminoethylaniline (5). To a round bottom flask 60 mg (0.170 mmol) 4 was dissolved in 4 mL of dichloroethane. To this solution 88 μL (0.850 mmol) of diethylamine and 72.1 mg (0.340 mmol) of $NaHB(OAc)_3$ were sequentially added and stirred at room temperature for 2 h. Ethyl acetate and distilled water were added and the organic layer was washed with water twice and brine once, then dried with Na_2SO_4, filtered and concentrated to give 62.6 mg of the crude product 5 which was used without further purification.

Diethylaminoethylaniline dihydrochloride (6). To a round bottom flask, 62.6 mg (0.153 mmol) of 5 was dissolved in 1 mL of methanol. To this solution 1 mL of 4 N HCl in dioxane was added slowly, stirred at room temperature for 1 h and concentrated to afford a quantitative amount (52.7 mg) of 6.

Bromopyrazolopyrimidine (8). To a round bottom flask, 52.7 mg (0.153 mmol) of 6, 3 mL of THF and 88.5 μL (0.635 mmol) of NEt_3 were added. To this suspension, 29.8 mg (0.127 mmol) of 7 were added and stirred at 65 °C for 30 minutes. The crude reaction was concentrated. Ethyl acetate and distilled water were added and the organic layer was washed with water twice and brine once. The organic layer was dried with Na_2SO_4, filtered, and concentrated. The crude material was purified by preparative HPLC to afford 16.4 mg of final product 8 (25%).

Observed M+H: 508.1

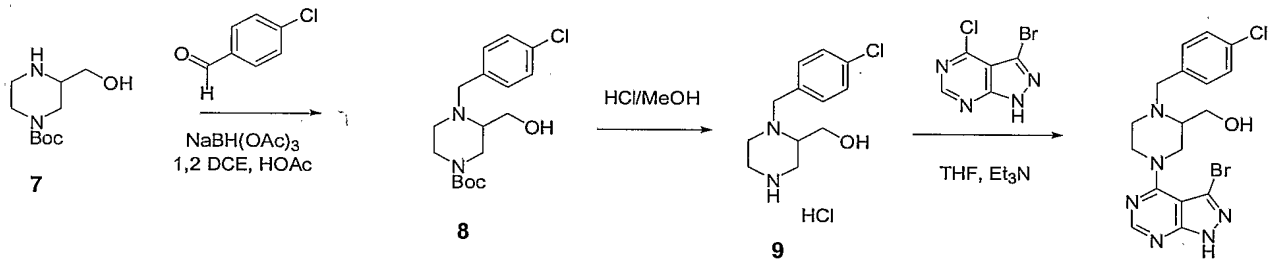
NMR, DMSO-d6, HCl salt: δ 10.43 (br. s, 1H), 8.30 (s, 1H), 7.22 (d, 2H), 7.03 (d, 2H), 4.60 (d, 2H), 4.01 (m, 1H), 3.63 (m, 2H), 3.29 (m, 2H), 3.14 (m, 4H), 3.02 (m, 2H), 1.84 (m, 4H), 1.19 (t, 6H) ppm.



[1-(3-Bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-piperidin-4-yl]-(4-chloro-phenyl)-carbamic acid 2-dimethylamino-ethyl ester:

Observed M+H: 524.1

NMR, DMSO-d6, HCl salt: δ 10.66 (br s, 1H), 8.29 (s, 1H), 7.46 (d, 2H), 7.29 (d, 2H), 4.51-4.48 (m, 3H), 4.34 (m, 2H), 3.29-3.23 (m, 4H), 2.67-2.45 (obs s, 6H), 2.01 (d, 2H), 1.47-1.41 (m, 2H) ppm.



7 8 9 10

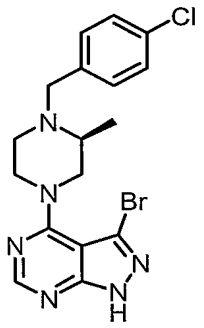
4-(4-Chloro-benzyl)-3-hydoxymethyl-piperazine-1-carboxylic acid *tert* butyl ester (8). To a 100 mL round bottom flask was added piperazine 7 (1.0g, 4.6 mmol, 1.0eq), 1,2 Dichloroethane (20 mL), 4-Chlorobenzaldehyde (644 mg, 4.6 mmol, 1.0 eq), acetic acid (1.0 mL), and $NaBH(OAc)_3$ (1.4g, 6.9 mmol, 1.5 eq.) The reaction was stirred overnight at RT, partitioned between EtOAc and water, washed with brine, dried with Na_2SO_4, concentrated, and column purified with 1:1 EtOAc:Hexanes to give 525 mg of pure 8 (33 % yield).

Observed M+H: 341.2

^{1}HNMR (*d6*-DMSO): 7.35 (dd, 4H), 4.0 (d, 1H), 3.98 (dd, 1H), 3.60 (m, 2H), 3.4 (d, 4H), 3.8 (m, 4H), 2.15 (m, 1H), 1.6 (s, 9H) ppm.

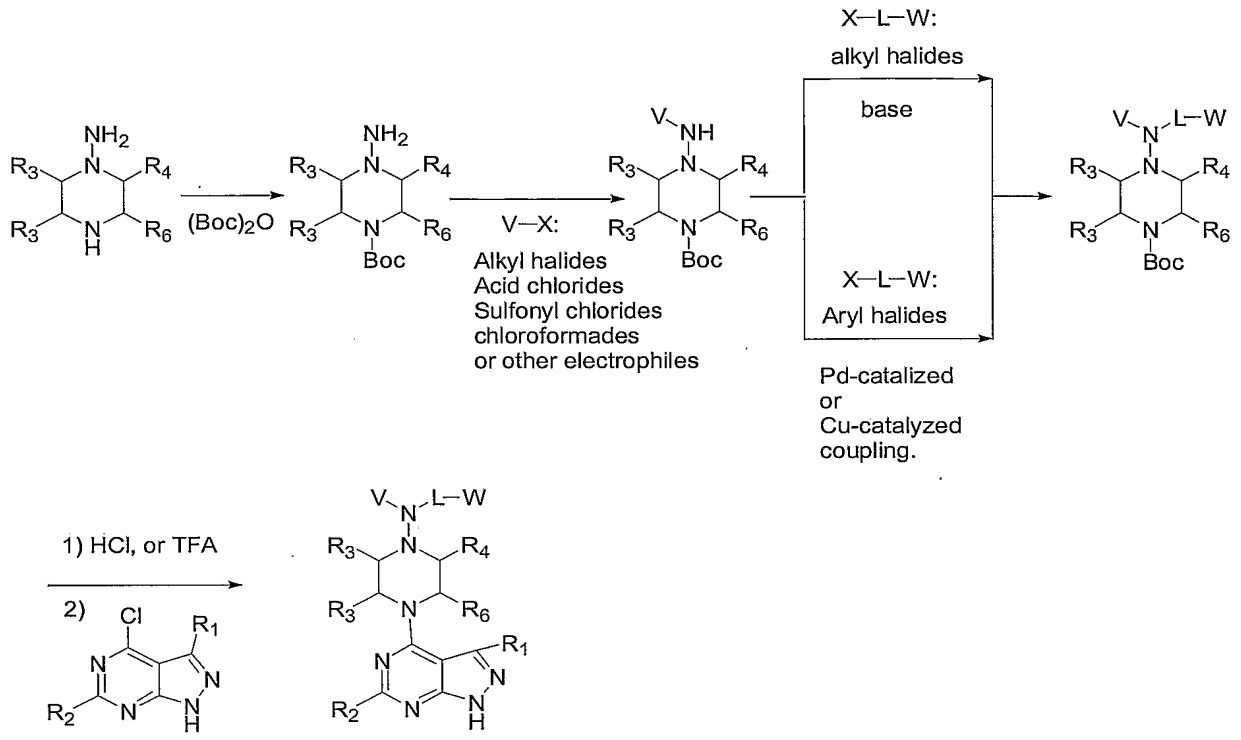
[4-(3-Bromo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-1-(4-Chloro-benzyl)-piperazin-2-yl]-methanol (10). To a round bottom flask was added 8 (100 mg, 0.29 mmol, 1.0eq), MeOH (1.0mL), and 4N HCl in dioxane (1.0 mL). The reaction was stirred at RT for 1 hr, concentrated on rotary evaporator and placed on high vacuum for 1 hr. The resulting de-boc'ed residue was dissolved in THF (5mL), and Et_3N (0.1 mL) before adding 3-Bromo-4-Chloro-1*H*-pyrazolo[3,4-*d*]pyrimidine (52 mg, 0.25 mmol, 0.9 eq). The mixture was heated to 65°C for 30 min., concentrated via rotary evaporation, dissolved in 4 mL DMSO and purifed via Prep HPLC using 20:80% gradient, 11 min run time, 40mL/min. After lyopholization, 60 mg of 8 was recovered as a solid.

Observed M+H, Bromine isotope: 437,439 (1:1)
^{1}HNMR (*d6*-DMSO): δ 10.0 (br s, 1H), 8.41 (s, 1H), 7.58 (m, 4H), 4.8 (br d, 1H), 4.70 (d, 2H), 4.50 (br d, 2H), 4.20 (m, 2H), 3.20 (m, 4H) ppm.



3-Bromo-4-[4-(4-chloro-benzyl)-3-methyl-piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine:
Observed M+H: 422.9
NMR, DMSO-d_6, TFA salt: δ 10.26 (br s, 1H), 8.44 (s, 1H), 7.59-7.57 (m, 4H), 4.81 (m, 1H), 4.56-4.45 (m, 3H), 4.18 (m, 1H), 3.58 (m, 1H), 3.39-3.33 (m, 2H), 3.19 (s, 2H), 1.53 (s, 3H) ppm.

Example 2



N-Amino-Piperazine derivatives are prepared according to the general synthetic route above in light of the methods of preparation set forth in Example 1. The compounds of Example 2 are prepared according to Formula I, wherein R_1-R_6, Q_1, Q_2, L, V and W are as described above and Q_1=Q_2=N.

Biochemical Assays

[0181] Kinase assays were performed by measurement of incorporation of γ-^{33}P ATP into immobilized myelin basic protein (MBP). High binding white 384 well plates (Greiner) were coated with MBP (Sigma #M-1891) by incubation of 60µl/well of 20µg/ml MBP in Tris-buffered saline (TBS; 50mM Tris pH 8.0, 138mM NaCl, 2.7mM KCl) for 24 hours at 4° C. Plates were washed 3X with 100µl TBS. Kinase reactions were carried out in a total volume of 34µl in kinase buffer (5mM Hepes pH 7.6, 15mM NaCl, 0.01% bovine gamma globulin (Sigma #I-5506), 10mM $MgCl_2$, 1mM DTT, 0.02% TritonX-100). Compound dilutions were

performed in DMSO and added to assay wells to a final DMSO concentration of 1%. Each data point was measured in duplicate, and at least two duplicate assays were performed for each individual compound determination. Enzyme was added to final concentrations of 10nM or 20nM, for example. A mixture of unlabeled ATP and γ-^{33}P ATP was added to start the reaction ($2x10^6$ cpm of γ-^{33}P ATP per well (3000Ci/mmole) and either 10μM or 30μM unlabeled ATP, typically. The reactions were carried out for 1 hour at room temperature with shaking. Plates were washed 7x with TBS, followed by the addition of 50μl/well scintillation fluid (Wallac). Radioactivity was measured using a Wallac Trilux counter. This is only one format of such assays, various other formats are possible, as known to one of ordinary skill in the art.

[0182] The above assay procedure can be used to determine the IC_{50} for inhibition and/or the inhibition constant, K_i. The IC_{50} is defined as the concentration of compound required to reduce the enzyme activity by 50% under the conditions of the assay. Exemplary compositions have IC_{50}'s of, for example, less than about 100 μM, less than about 10 μM, less than about 1 μM, and further for example having IC_{50}'s of less than about 100 nM, and still further, for example, less than about 10 nM. The K_i for a compound may be determined from the IC_{50} based on three assumptions. First, only one compound molecule binds to the enzyme and there is no cooperativity. Second, the concentrations of active enzyme and the compound tested are known (i.e., there are no significant amounts of impurities or inactive forms in the preparations). Third, the enzymatic rate of the enzyme-inhibitor complex is zero. The rate (i.e., compound concentration) data are fitted to equation (1) below; where V is the observed rate, V_{max}, is the rate of the free enzyme, I_0 is the inhibitor concentration, E_0 is the enzyme concentration, and K_d is the dissociation constant of the enzyme-inhibitor complex.

$$V = V_{\max} E_0 \left[I - \frac{(E_0 + I_0 + K_d) - \sqrt{(E_0 + I_0 + K_d)^2 - 4E_0 I_0}}{2E_0} \right]$$

Equation (1)

Kinase Specific Assays:

[0183] Kinase activity and compound inhibition are investigated using one or more of the three assay formats described below. The ATP concentrations for each assay are selected to be close to the Michaelis-Menten constant (K_M) for each individual kinase. Dose-response experiments

are performed at 10 different inhibitor concentrations in a 384-well plate format. The data are fitted to four-parameter equation (2) below; where Y is the observed signal, X is the inhibitor concentration, Min is the background signal in the absence of enzyme (0% enzyme activity), Max is the signal in the absence of inhibitor (100% enzyme activity), IC_{50} is the inhibitor concentration at 50% enzyme inhibition and H represents the empirical Hill's slope to measure the cooperativity. Typically H is close to unity.

$$Y = Min + (Max - Min) / (1 + (X/IC_{50})^{\wedge}H)$$

Equation (2)

p70S6 Kinase Assay

[0184] Biochemical activity of p70S6 kinase was assessed using a Luciferase-Coupled Chemiluminescent Kinase assay (LCCA) format. Kinase activity was measured as the percent ATP remaining following the kinase reaction. Remaining ATP was detected by luciferase-luciferin-coupled chemiluminescence. Specifically, the reaction was initiated by mixing test compounds, 5μM ATP, 5μM RRRLSSLRA peptide and 12nM p70S6K (baculovirus expressed human p70S6 kinase domainresidues 1-421, containing a T412E mutation) in a 20uL assay buffer (20mM Tris-HCL pH 7.5, 10mM $MgCl_2$, 0.02% Triton X-100, 100mM DTT, 2mM $MnCl_2$). The mixture is incubated at ambient temperature for 2hours after which 20μL luciferase-luciferin mix is added and the chemiluminescent signal read using a Wallac Victor^2 reader. The luciferase-luciferin mix consists of 50 mM HEPES, pH 7.8, 8.5μg/mL oxalic acid (pH 7.8), 5 (or 50) mM DTT, 0.4% Triton X-100, 0.25 mg/mL coenzyme A, 63 uM AMP, 28 μg/mL luciferin and 40,000 units/mL luciferase.

Akt1 Kinase Assay

[0185] Biochemical activity of Akt1 kinase was assessed using a Luciferase-Coupled Chemiluminescent Kinase assay (LCCA) format. Kinase activity was measured as the percent ATP remaining following the kinase reaction. Remaining ATP was detected by luciferase-luciferin-coupled chemiluminescence. Specifically, the reaction was initiated by mixing test compounds, 1μM ATP, 5μM crosstide peptide and 1.3nM Akt1 (baculovirus expressed human Akt1 kinase domain residues R144-A480, activated with PDK1) in a 20uL assay buffer (20mM Tris-HCL pH 7.5, 10mM MgCl2, 0.01% Triton X-100, 1mM DTT, 3mM MnCl2). The mixture

is incubated at ambient temperature for 3 hours after which 20μL luciferase-luciferin mix is added and the chemiluminescent signal read using a Wallac Victor2 reader. The luciferase-luciferin mix consists of 50 mM HEPES, pH 7.8, 8.5 μg/mL oxalic acid (pH 7.8), 5 (or 50) mM DTT, 0.4% Triton X-100, 0.25 mg/mL coenzyme A, 63 uM AMP, 28 μg/mL luciferin and 40,000 units/mL luciferase.

Akt2 Kinase Assay

[0186] Biochemical activity of Akt2 kinase was assessed using a Luciferase-Coupled Chemiluminescent Kinase assay (LCCA) format. Kinase activity was measured as the percent ATP remaining following the kinase reaction. Remaining ATP was detected by luciferase-luciferin-coupled chemiluminescence. Specifically, the reaction was initiated by mixing test compounds, 2μM ATP, 5μM crosstide peptide and 10nM Akt2 (baculovirus expressed human Akt2 kinase domain residues K146-R480) in a 20uL assay buffer (20mM Tris-HCL pH 7.5, 10mM MgCl2, 0.03% Triton X-100, 1mM DTT, 3mM MnCl2). The mixture is incubated at ambient temperature for 2 hours after which 20 μL luciferase-luciferin mix is added and the chemiluminescent signal read using a Wallac Victor2 reader. The luciferase-luciferin mix consists of 50 mM HEPES, pH 7.8, 8.5 μg/mL oxalic acid (pH 7.8), 5 (or 50) mM DTT, 0.4% Triton X-100, 0.25 mg/mL coenzyme A, 63 uM AMP, 28 μg/mL luciferin and 40,000 units/mL luciferase.

Structure Activity Relationships

[0187] Table 2 shows structure activity relationship data for selected compounds of the invention. Inhibition is indicated as IC_{50} with the following key: A = IC_{50} less than 50 nM, B = IC_{50} greater than 50 nM, but less than 500 nM, C = IC_{50} greater than 500 nM, but less than 2000 nM, and D = IC_{50} equal to, or greater than 2,000 nM.

Table 2

Entry	Name	p70S6K	Akt-1	Akt-2
1	[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methanol	A	A	
2	2-{[[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]oxy}-N,N-dimethylethanamine	A	A	B
3	3-{[[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]oxy}-N,N-dimethylpropan-1-amine	A	A	
4	3-bromo-4-{4-[(4-bromophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	A	B	
5	{4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-1-[(4-chlorophenyl)methyl]piperazin-2-yl}methanol	A	B	
6	N'-[[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]-N,N-diethylethane-1,2-diamine	A	A	
7	3-bromo-4-(4-{[4-(1,1-dimethylethyl)phenyl]methyl}piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine	A	D	D
8	4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-1-[(4-chlorophenyl)methyl]piperazin-2-one	A	B	
9	2-[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-(4-chlorophenyl)-N-[2-(dimethylamino)ethyl]acetamide	A	A	
10	N-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-N-(4-chlorophenyl)-N',N'-diethylpropane-1,3-diamine	A	A	
11	3-bromo-4-(4-{[4-(trifluoromethyl)phenyl]methyl}piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine	A	C	D
12	N-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-N-(4-chlorophenyl)-N'-[2-(dimethylamino)ethyl]urea	A	A	
13	N-[[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]-N'-[2-(dimethylamino)ethyl]urea	A	A	
14	2-[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-2-oxopiperazin-1-yl]-2-(4-chlorophenyl)-N-[2-(dimethylamino)ethyl]acetamide	A	A	
15	2-(dimethylamino)ethyl [1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)carbamate	A	A	
16	3-bromo-4-{4-[(4-chloro-3-fluorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	A	B	
17	3-bromo-4-{4-[(4-chloro-2-fluorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	A	B	
18	N-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-N-(4-chlorophenyl)-N',N'-diethylethane-1,2-diamine	A	A	

Table 2

Entry	Name	p70S6K	Akt-1	Akt-2
19	3-bromo-4-{4-[(4-chlorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	A	B	D
20	[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-fluorophenyl)methanone	A	A	
21	N-[[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]-N',N'-diethyl-N-methylethane-1,2-diamine	A	A	
22	[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-fluorophenyl)methanol	A	B	
23	3-bromo-4-(4-{[2-fluoro-4-(trifluoromethyl)phenyl]methyl}piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine	A	B	
24	N-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-N-(4-chlorophenyl)-N~3~,N~3~-diethyl-beta-alaninamide	A	A	
25	2-{[[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-fluorophenyl)methyl]oxy}-N,N-dimethylethanamine	A	A	
26	N-[[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]-N~3~,N~3~-diethyl-beta-alaninamide	A	A	
27	3-bromo-4-{4-[(3,4-dichlorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	A	B	D
28	N-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-N-(4-chlorophenyl)-N'-[2-(dimethylamino)ethyl]ethanediamide	A	A	
29	N-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-N-(4-chlorophenyl)-2-(diethylamino)ethanesulfonamide	A	A	
30	4-[4-(biphenyl-4-ylmethyl)piperazin-1-yl]-3-bromo-1H-pyrazolo[3,4-d]pyrimidine	A	D	D
31	3-bromo-4-{(3S)-4-[(4-chlorophenyl)methyl]-3-methylpiperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	A	C	D
32	3-bromo-4-(4-{[4-(methyloxy)phenyl]methyl}piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine	A	C	D
33	4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-N-[3-(trifluoromethyl)phenyl]piperazine-1-carboxamide	A	D	D
34	3-bromo-4-{4-[(4-fluorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	A	C	D
35	N-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-N-(4-chlorophenyl)pent-4-enamide	A	B	
36	3-bromo-4-[4-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	A	D	D
37	4-[4-(1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]-3-bromo-1H-pyrazolo[3,4-d]pyrimidine	A	C	D
38	[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methanone	A	C	D
39	3-bromo-4-(4-{[4-(phenyloxy)phenyl]methyl}piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine	A	D	D
40	3-bromo-4-{4-[(3,4-dichlorophenyl)methyl]piperidin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	A	D	
41	4-{[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]methyl}-N,N-dimethylaniline	A	D	D

Table 2

Entry	Name	p70S6K	Akt-1	Akt-2
42	methyl 4-{[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]methyl}benzoate	A	D	
43	3-bromo-4-{4-[(2E)-3-phenylprop-2-enoyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	A	D	D
44	1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-4-[(4-chlorophenyl)methyl]-N-[3-(diethylamino)propyl]piperidine-4-carboxamide	A	B	
45	3-bromo-4-{4-[(2-bromophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	A	D	D
46	3-bromo-4-{4-[(2-chlorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	A	D	D
47	3-bromo-4-{4-[(2,4-dichlorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	A	C	D
48	3-bromo-4-{4-[(2-chloro-4-fluorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	A	D	D
49	1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-4-(4-chlorophenyl)-N-[3-(diethylamino)propyl]piperidine-4-carboxamide	A	C	
50	3-bromo-4-[4-(phenylmethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	B	D	D
51	2-[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-pyridin-2-ylacetamide	B	D	D
52	3-bromo-4-[4-(1H-imidazol-2-ylmethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	B	D	D
53	3-bromo-4-(4-{[3-(phenyloxy)phenyl]methyl}piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine	B	D	D
54	3-bromo-4-{4-[(3-methylphenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	B	D	D
55	3-{[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]methyl}benzonitrile	B	D	D
56	3-bromo-4-{4-[(2-chloro-6-fluorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	B	D	D
57	3-bromo-4-[4-(1-phenylethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	B	D	D
58	3-bromo-4-[4-(pyridin-4-ylmethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	B	D	D
59	1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-N-(4-chlorophenyl)piperidin-4-amine	B	D	
60	3-bromo-4-[4-(pyridin-3-ylmethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	B	D	D
61	3-bromo-4-(4-{[2,3,4-tris(methyloxy)phenyl]methyl}piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine	B	D	D
62	3-bromo-4-[4-({3-[(phenylmethyl)oxy]phenyl}methyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	B	D	D
63	3-bromo-4-[4-(naphthalen-1-ylmethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	B	D	D
64	3-bromo-4-(4-{[5-(4-chlorophenyl)furan-2-yl]methyl}piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine	C	D	D

Table 2

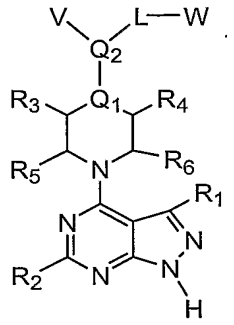
Entry	Name	p70S6K	Akt-1	Akt-2
65	3-bromo-4-[4-({4-[(4-fluorophenyl)oxy]-3-nitrophenyl}methyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	C	D	
66	3-bromo-4-[4-(furan-2-ylcarbonyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	C	D	D
67	3-bromo-4-[4-(1H-indol-6-ylcarbonyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	C	D	D
68	3-bromo-4-{4-[2-(2-thienyl)ethyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	C	D	D
69	3-bromo-4-[4-(3-pyrrolidin-1-ylpropyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	C	D	D
70	3-bromo-4-[4-(cyclohexylmethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	C	D	D
71	3-bromo-4-{4-[(10-chloroanthracen-9-yl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	C	D	D
72	3-bromo-4-[4-(1-methylpropyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	C	D	D
73	4-(4-{[4,6-bis(methyloxy)pyrimidin-2-yl]methyl}piperazin-1-yl)-3-bromo-1H-pyrazolo[3,4-d]pyrimidine	C	D	D
74	3-bromo-4-{4-[2-(methyloxy)ethyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	C	D	D
75	3-bromo-4-[4-(2-morpholin-4-yl-2-oxoethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	D	D	D
76	3-bromo-4-{4-[3-(methyloxy)propyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	D	D	D
77	4-{4-[[4,6-bis(methyloxy)pyrimidin-2-yl](phenyl)methyl]piperazin-1-yl}-3-bromo-1H-pyrazolo[3,4-d]pyrimidine	D	D	D
78	3-bromo-4-[4-(6,7,8,9-tetrahydro-5H-benzocyclohepten-5-yl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	D	D	D
79	3-bromo-4-[4-({4-[(phenylmethyl)oxy]phenyl}methyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	D	D	D
80	3-bromo-4-[4-({3-chloro-4-[(phenylmethyl)oxy]phenyl}methyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	D	D	
81	4-{[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]methyl}-N-(3-morpholin-4-ylpropyl)benzamide	D	D	
82	4-{[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]methyl}-N-[3-(methyloxy)propyl]benzamide	D	D	
83	2-[({4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-1-[(4-chlorophenyl)methyl]piperazin-2-yl}methyl)oxy]-N,N-dimethylethanamine	D	D	
84	3-bromo-4-[4-({4-[(4-chlorophenyl)oxy]-3-nitrophenyl}methyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	D	D	
85	2-[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N,N-dimethylacetamide	D	D	D
86	2-{[(R)-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]oxy}-N,N-dimethylethanamine	A	A	
87	N-(4-bromo-3-fluorophenyl)-N-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-N'-[2-(dimethylamino)ethyl]urea	A	A	

Table 2

Entry	Name	p70S6K	Akt-1	Akt-2
88	2-({(R)-(4-chlorophenyl)[1-(3-ethyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]methyl}oxy)-N,N-dimethylethanamine	A	A	
89	2-{[(S)-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]oxy}-N,N-dimethylethanamine	A	A	
90	3-bromo-4-(4-{(R)-(4-chlorophenyl)[(2-pyrrolidin-1-ylethyl)oxy]methyl}piperidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine	A	A	
91	1-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-1-(4-chlorophenyl)-4-(dimethylamino)butan-1-ol	A	A	
92	2-{[(R)-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chloro-3-fluorophenyl)methyl]oxy}-N,N-dimethylethanamine	A	A	
93	3-bromo-4-(4-{(R)-(4-chlorophenyl)[(2-piperidin-1-ylethyl)oxy]methyl}piperidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine	A	A	
94	4-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-4-(4-chlorophenyl)-N,N-dimethylbutan-1-amine	A	A	
95	3-bromo-4-(4-{(R)-(4-chlorophenyl)[(2-morpholin-4-ylethyl)oxy]methyl}piperidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine	A	A	
96	1-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-1-(4-fluorophenyl)-N-(furan-2-ylmethyl)-N-methylmethanamine	B	C	
97	1-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-1-(4-fluorophenyl)-N-methyl-N-(pyridin-2-ylmethyl)methanamine	B	C	
98	4-{[{[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-fluorophenyl)methyl}(methyl)amino]methyl}-N,N-dimethylaniline	A	B	
99	[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl](1H-indol-6-yl)methanol	B	C	
100	3-bromo-4-(4-{(R)-(4-chloro-3-fluorophenyl)[(2-pyrrolidin-1-ylethyl)oxy]methyl}piperidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine	A	A	
101	3-bromo-4-{4-[(4-chlorophenyl)oxy]piperidin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	B	C	
102	2-{[(R)-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]oxy}-N,N-diethylethanamine	A	A	
103	2-{[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]oxy}-5-chloro-N-(2-pyrrolidin-1-ylethyl)aniline	B	B	

What is claimed is:

1. A compound according to Formula I,



and pharmaceutically acceptable salts, hydrates and prodrugs thereof wherein:

R_1 is H, halo, cyano, aryl, heteroaryl, C_{1-4} alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein the aryl, heteroaryl, alkyl, alkenyl and alkynyl are optionally substituted with one or two groups independently selected from CO_2R_{10}, $CONR_{10}R_{11}$, OR_{10}, and $NR_{10}R_{11}$;

R_2 is H, NH_2, SH, OH, or C_1-C_2 alkyl;

R_3, R_4, R_5, and R_6 are each independently H, oxo, CO_2R_{10}, $CONR_{10}R_{11}$, C_{1-4} alkyl, C_1-C_6 alkoxy, or C_1-C_6 alkoxy-C_1-C_4 alkyl, wherein the C_1-C_4 alkyl, C_1-C_6 alkoxy and C_1-C_6 alkoxy-C_1-C_4 alkyl in each group are independently optionally substituted with 1 or 2 substituents independently selected from CO_2R_{10}, $CONR_{10}R_{11}$, OR_{10}, and $NR_{10}R_{11}$, or

R_3 and R_5 together with the carbons to which they are attached form a C_3-C_7 carbocyclic ring, wherein the ring is optionally substituted with H, halo, cyano, nitro, or amino,

R_4 and R_6 together with the carbons to which they are attached form a C_3-C_7 carbocyclic ring, wherein the ring is optionally substituted with H, halo, cyano, nitro, or amino R_3 and R_6 together with the carbons to which they are attached form a bridged C_5-C_7 carbocyclic ring, wherein the ring is optionally substituted with H, halo, cyano, nitro, or amino, or

R_4 and R_5 together with the carbons to which they are attached form a bridged C_5-C_7 carbocyclic ring, wherein the ring is optionally substituted with H, halo, cyano, nitro, or amino;

L is C_{0-4} alkyl, C_2-C_6 alkenyl, -N(R_{12})-, -C(O)N(R_{12})-, -N(R_{12})C(O)-, -C(O)-, -O-$(CH_2)_n$-, or -$(CH_2)_n$-O-, wherein n is 1-4;

Q_1 is N or CR_{13}, wherein R_{13} is H or $C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$;

Q_2 is a bond, CR_{14}, O or N, wherein R_{14} is H, OH, C_1-$_4$ alkyl, C_1-$_4$ alkoxy, $NR_{15}R_{15}$, wherein R_{15} is H or C_1-$_4$ alkyl, or Q_2 and V together form C(=O);

when Q_2 is a bond,

V is absent and R_{13} is not H;

when Q_1 is CR_{13} and Q_2 is CH,

V is H, OH, NH_2, C_1-C_6 alkoxy, $NR_{10}R_{11}$, $O(CH_2)_nNR_{10}R_{11}$, $O(CH_2)_n$ attached to a C or N of a 4-7 membered heterocyclyl, $NR_{12}(CH_2)_nNR_{10}R_{11}$, $NR_{12}C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$, $NR_{12}C(O)(CH_2)_nNR_{10}R_{11}$, $(CH_2)_mO(CH_2)_nNR_{10}R_{11}$, $(CH_2)_mNR_{12}(CH_2)_nNR_{10}R_{11}$, $(CH_2)_mCHR_{12}(CH_2)_nNR_{10}R_{11}$, C_{1-4} alkyl optionally substituted with OH or $NR_{10}R_{11}$, or

V is a 4-7 membered unsaturated cyclic containing 1-3 atom of O or N, or

V is a bicyclic solublizing group;

when Q_1 is N and Q_2 is CH, or when Q_1 is CR_{13} and Q_2 is O or N,

V is H, $(CH_2)_mO(CH_2)_nNR_{10}R_{11}$, $(CH_2)_mNR_{12}(CH_2)_nNR_{10}R_{11}$, $(CH_2)_mCHR_{12}(CH_2)_nNR_{10}R_{11}$, $C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$, $C(O)(CH_2)_nNR_{10}R_{11}$, $C(O)O(CH_2)_nNR_{10}R_{11}$, $C(O)C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$, $SO_2(CH_2)_nNR_{10}R_{11}$, C(O)-$C_2$-$C_6$ alkenyl, or C_{1-4} alkyl optionally substituted with OH or $NR_{10}R_{11}$, or

V is a 4-7 membered saturated or unsaturated cyclic or heterocyclic containing 1-3 atoms of O or N, optionally substituted with 1 or 2 C_1-C_3 alkoxy groups or

V is a "bicyclic solublizing group";

m is 1-3,

n is 1-4,

W is C_1-C_6 alkyl, $NR_{10}R_{11}$, or W is

aryl, C_3-C_7 cycloalkyl, heterocyclyl, heteroaryl, or 5-12 membered fused bicylic or tricyclic saturated, partially saturated, or usaturated ring system containing 0-4 ring atoms selected from N, O, and S, wherein each aryl, cycloalkyl, heterocyclyl, heteroaryl, and fused bicyclic or tricyclic ring system is optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2, CF_3, OH, $NR_{10}R_{11}$, C_1-C_6 alkoxy, C_1-C_6 alkyl, NO_2, $C(O)OC_1$-C_6 alkyl, $C(O)NR_{12}$-C_1-C_6 alkoxy, $C(O)NR_{12}$-heterocyclyl, aryl, O-aryl, O-CH_2-aryl, N-aryl, wherein each aryl substituent is optionally further substituted with halo, or

V, Q_2, L, and W together form an aryl ring, heteroaryl ring, C_3-C_7 cycloalkyl ring, heterocyclyl ring, or a 5-12 membered fused bicylic or tricyclic saturated, partially saturated or usaturated ring system containing 0-4 ring atoms selected from N, O, and S, wherein each ring or ring system is optionally substituted with 1, 2, or 3 groups independently selected from halo, CN, NO_2, CF_3, OH, $NR_{10}R_{11}$, C_1-C_6 alkoxy, C_1-C_6 alkyl, NO_2, $C(O)OC_1$-C_6 alkyl, $C(O)NR_{12}$-C_1-C_6 alkoxy, $C(O)NR_{12}$-heterocyclyl, aryl, O-aryl, NH-aryl, wherein each aryl substituent is optionally further substituted with halo; and

R_{10}, R_{11} and R_{12} are each independently H or C_1-$_6$ alkyl which is optionally substituted with aryl or heteroaryl.

2. A compound according to Claim 1, wherein the following compounds are excluded as compounds of Formula I:

4-(4-(2-fluorophenyl)piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine;

4-(4-(3-chlorophenyl)piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine;

ethyl 4-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate;

tert-butyl 4-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate; and

N-(4-phenoxyphenyl)-4-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazine-1-carboxamide.

3. A compound according to Formula II, which are compounds of Formula I wherein R_1 is not hydrogen.

4. A compound according to Claim 3, wherein R_1 is halo, C_1-C_4 alkyl, OH, cyano, or amino.

5. A compound according to Claim 4, wherein R_1 is halo.

6. A compound according to Claim 5, wherein R_1 is bromo.

7. A compound according to Claim 6, wherein R_2 is H.

8. A compound according to Claim 7, wherein R_3, R_4, R_5, and R_6, are each H.

9. A comound according to Formula III, which are compounds of Formula I or Formula II wherein Q_1 is CH and Q_2 is CH.

10. A compound according to Claim 9, wherein L is a bond.

11. A compound according to Claim 10, wherein W is aryl optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2, CF_3, OH, $NR_{10}R_{11}$, C_1-C_6 alkoxy, C_1-C_6 alkyl, NO_2, $C(O)OC_1$-C_6 alkyl, $C(O)NR_{12}$-C_1-C_6 alkoxy, $C(O)NR_{12}$-heterocyclyl, aryl, O-aryl, O-CH_2-aryl, NH-aryl, wherein each aryl substituent is optionally further substituted with halo.

12. A compound according to Claim 11, wherein wherein W is phenyl optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2, CF_3, OH, $NR_{10}R_{11}$, C_1-C_6 alkoxy, C_1-C_6 alkyl, NO_2, $C(O)OC_1$-C_6 alkyl, $C(O)NR_{12}$-C_1-C_6 alkoxy, $C(O)NR_{12}$-heterocyclyl, aryl, O-aryl, O-CH_2-aryl, N-aryl, wherein each aryl substituent is optionally further substituted with halo.

13. A compound according to Claim 12, wherein W is phenyl optionally substituted with 1, or 2 substituents independently selected from halo, CF_3, C_1-$_4$ alkyl, and C_1-C_4 alkoxy.

14. A compound according to Claim 13, wherein W is phenyl optionally substituted with 1, or 2 substituents independently selected from F, Cl and Br.

15. A compound according to Claim 14, wherein V is H, OH, $O(CH_2)_nNR_{10}R_{11}$, $NR_{12}(CH_2)_nNR_{10}R_{11}$, $NR_{12}C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$, or $NR_{12}C(O)(CH_2)_nNR_{10}R_{11}$.

16. A compound according to Claim 15, wherein V is H, OH, $O(CH_2)_nNR_{10}R_{11}$, $NR_{12}(CH_2)_nNR_{10}R_{11}$, $NR_{12}C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$, or $NR_{12}C(O)(CH_2)_nNR_{10}R_{11}$ and R_{10} and R_{11} are each CH_3.

17. A compound according to Claim 16, wherein R_1 is H, halo or C_1-C_2 alkyl and R_2 is H.

18. A compound according to Claim 17, wherein R_3, R_4, R_5, and R_6, are each H.

19. A compound according to Formula IV, which are compounds of Formula I or Formula II wherein Q_1 is N and Q_2 is CH.

20. A compound according to Claim 19, wherein L is a bond.

21. A compound according to Claim 20, wherein W is aryl optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2, CF_3, OH, $NR_{10}R_{11}$, C_1-C_6 alkoxy, C_1-C_6 alkyl, NO_2, $C(O)OC_1$-C_6 alkyl, $C(O)NR_{12}$-C_1-C_6 alkoxy, $C(O)NR_{12}$-heterocyclyl, aryl, O-aryl, O-CH_2-aryl, N-aryl, wherein each aryl substituent is optionally further substituted with halo.

22. A compound according to Claim 21, wherein W is phenyl optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2, CF_3, OH, $NR_{10}R_{11}$, C_1-C_6 alkoxy, C_1-C_6 alkyl, NO_2, $C(O)OC_1$-C_6 alkyl, $C(O)NR_{12}$-C_1-C_6 alkoxy, $C(O)NR_{12}$-heterocyclyl, aryl, O-aryl, O-CH_2-aryl, N-aryl, wherein each aryl substituent is optionally further substituted with halo.

23. A compound according to Claim 22, wherein W is phenyl optionally substituted with 1, or 2 substituents independently selected from halo, CF_3, C_1-$_4$ alkyl, and C_1-C_4 alkoxy.

24. A compound according to Claim 23, wherein W is phenyl optionally substituted with 1, or 2 substituents independently selected from F, Cl and Br.

25. A compound according to Claim 24, wherein V is H, $C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$, or C_{1-4} alkyl.

26. A compound according to Claim 25, wherein V is H, $C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$, or C_{1-4} alkyl and R_{10} and R_{11} are each CH_3.

27. A compound according to Claim 26, wherein V is H.

28. A compound according to Claim 27, wherein R_1 is halo and R_2 is H.

29. A compound according to Claim 28, wherein R_3, R_4, R_5, and R_6, are each H.

30 A compound of Formula V, which are compounds of Formula I or Formula II wherein Q_1 is CH and Q_2 is N.

31. A compound of Claim 30, wherein L is a bond.

32. A compound of Claim 31, wherein W is aryl optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2, CF_3, OH, $NR_{10}R_{11}$, C_1-C_6 alkoxy, C_1-C_6 alkyl, NO_2, $C(O)OC_1$-C_6 alkyl, $C(O)NR_{12}$-C_1-C_6 alkoxy, $C(O)NR_{12}$-heterocyclyl, aryl, O-aryl, O-CH_2-aryl, N-aryl, wherein each aryl substituent is optionally further substituted with halo.

33. A compound of Claim 32, wherein W is phenyl optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2, CF_3, OH, $NR_{10}R_{11}$, C_1-C_6 alkoxy, C_1-

C_6 alkyl, NO_2, $C(O)OC_1$-C_6 alkyl, $C(O)NR_{12}$-C_1-C_6 alkoxy, $C(O)NR_{12}$-heterocyclyl, aryl, O-aryl, O-CH_2-aryl, N-aryl, wherein each aryl substituent is optionally further substituted with halo.

34. A compound of Claim 33, wherein W is phenyl optionally substituted with 1, or 2 substituents independently selected from halo, CF_3, C_1-$_4$ alkyl, and C_1-C_4 alkoxy.

35. A compound of Claim 34, wherein W is phenyl optionally substituted with 1, or 2 substituents independently selected from F, Cl and Br.

36. A compound of Claim 35, wherein V is H, $C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$, $C(O)(CH_2)_nNR_{10}R_{11}$, $C(O)O(CH_2)_nNR_{10}R_{11}$, $C(O)C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$, $SO_2(CH_2)_nNR_{10}R_{11}$, C(O)-$C_2$-$C_6$ alkenyl, or C_1-$_4$ alkyl optionally substituted with $NR_{10}R_{11}$.

37. A compound of Claim 36, wherein V is H, $C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$, $C(O)(CH_2)_nNR_{10}R_{11}$, $C(O)O(CH_2)_nNR_{10}R_{11}$, $C(O)C(O)NR_{12}(CH_2)_nNR_{10}R_{11}$, $SO_2(CH_2)_nNR_{10}R_{11}$, C(O)-$C_2$-$C_6$ alkenyl, or C_1-$_4$ alkyl optionally substituted with $NR_{10}R_{11}$ and R_{10} and R_{11} are each CH_3.

38. A compound of Claim 37, wherein R_1 is halo and R_2 is H.

39. A compound of Claim 38, wherein wherein R_3, R_4, R_5, and R_6, are each H.

40. A compound of Formula VI, which are compounds of Formula I or Formula II wherein Q_1 is CH or N, and Q_2 and V together form C(=O).

41. A compound of Claim 40, wherein L is a bond.

42. A compound of Claim 41, wherein W is aryl optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2, CF_3, OH, $NR_{10}R_{11}$, C_1-C_6 alkoxy, C_1-C_6 alkyl, NO_2, $C(O)OC_1$-C_6 alkyl, $C(O)NR_{12}$-C_1-C_6 alkoxy, $C(O)NR_{12}$-heterocyclyl, aryl, O-aryl, O-CH_2-aryl, N-aryl, wherein each aryl substituent is optionally further substituted with halo.

43. A compound of Claim 42, wherein W is phenyl optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2, CF_3, OH, $NR_{10}R_{11}$, C_1-C_6 alkoxy, C_1-C_6 alkyl, NO_2, $C(O)OC_1$-C_6 alkyl, $C(O)NR_{12}$-C_1-C_6 alkoxy, $C(O)NR_{12}$-heterocyclyl, aryl, O-aryl, O-CH_2-aryl, N-aryl, wherein each aryl substituent is optionally further substituted with halo.

44. A compound of Claim 43, wherein W is phenyl optionally substituted with 1, or 2 substituents independently selected from halo, CF_3, C_1-$_4$ alkyl, and C_1-C_4 alkoxy.

45. A compound of Claim 44, wherein W is phenyl optionally substituted with 1, or 2 substituents independently selected from F, Cl and Br.

46. A compound of Claim 45, wherein R_1 is halo and R_2 is H.

47. A compound of Claim 46, wherein R_3, R_4, R_5, and R_6, are each H.

48. The compound according to claim 1, selected from Table 3.

Table 3

Entry	Name
1	[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methanol
2	2-{[[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]oxy}-N,N-dimethylethanamine
3	3-{[[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]oxy}-N,N-dimethylpropan-1-amine
4	3-bromo-4-{4-[(4-bromophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine
5	{4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-1-[(4-chlorophenyl)methyl]piperazin-2-yl}methanol
6	N'-[[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]-N,N-diethylethane-1,2-diamine
7	3-bromo-4-(4-{[4-(1,1-dimethylethyl)phenyl]methyl}piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine
8	4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-1-[(4-chlorophenyl)methyl]piperazin-2-one
9	2-[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-(4-chlorophenyl)-N-[2-(dimethylamino)ethyl]acetamide
10	N-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-N-(4-chlorophenyl)-N',N'-diethylpropane-1,3-diamine
11	3-bromo-4-(4-{[4-(trifluoromethyl)phenyl]methyl}piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine
12	N-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-N-(4-chlorophenyl)-N'-[2-(dimethylamino)ethyl]urea
13	N-[[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]-N'-[2-(dimethylamino)ethyl]urea
14	2-[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-2-oxopiperazin-1-yl]-2-(4-chlorophenyl)-N-[2-(dimethylamino)ethyl]acetamide
15	2-(dimethylamino)ethyl [1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)carbamate
16	3-bromo-4-{4-[(4-chloro-3-fluorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine
17	3-bromo-4-{4-[(4-chloro-2-fluorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine

Table 3

Entry	Name
18	N-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-N-(4-chlorophenyl)-N',N'-diethylethane-1,2-diamine
19	3-bromo-4-{4-[(4-chlorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine
20	[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-fluorophenyl)methanone
21	N-[[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]-N',N'-diethyl-N-methylethane-1,2-diamine
22	[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-fluorophenyl)methanol
23	3-bromo-4-(4-{[2-fluoro-4-(trifluoromethyl)phenyl]methyl}piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine
24	N-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-N-(4-chlorophenyl)-N~3~,N~3~-diethyl-beta-alaninamide
25	2-{[[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-fluorophenyl)methyl]oxy}-N,N-dimethylethanamine
26	N-[[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]-N~3~,N~3~-diethyl-beta-alaninamide
27	3-bromo-4-{4-[(3,4-dichlorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine
28	N-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-N-(4-chlorophenyl)-N'-[2-(dimethylamino)ethyl]ethanediamide
29	N-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-N-(4-chlorophenyl)-2-(diethylamino)ethanesulfonamide
30	4-[4-(biphenyl-4-ylmethyl)piperazin-1-yl]-3-bromo-1H-pyrazolo[3,4-d]pyrimidine
31	3-bromo-4-{(3S)-4-[(4-chlorophenyl)methyl]-3-methylpiperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine
32	3-bromo-4-(4-{[4-(methyloxy)phenyl]methyl}piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine
33	4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-N-[3-(trifluoromethyl)phenyl]piperazine-1-carboxamide
34	3-bromo-4-{4-[(4-fluorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine
35	N-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-N-(4-chlorophenyl)pent-4-enamide
36	3-bromo-4-[4-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine
37	4-[4-(1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]-3-bromo-1H-pyrazolo[3,4-d]pyrimidine
38	[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methanone
39	3-bromo-4-(4-{[4-(phenyloxy)phenyl]methyl}piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine

Table 3

Entry	Name
40	3-bromo-4-{4-[(3,4-dichlorophenyl)methyl]piperidin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine
41	4-{[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]methyl}-N,N-dimethylaniline
42	methyl 4-{[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]methyl}benzoate
43	3-bromo-4-{4-[(2E)-3-phenylprop-2-enoyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine
44	1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-4-[(4-chlorophenyl)methyl]-N-[3-(diethylamino)propyl]piperidine-4-carboxamide
45	3-bromo-4-{4-[(2-bromophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine
46	3-bromo-4-{4-[(2-chlorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine
47	3-bromo-4-{4-[(2,4-dichlorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine
48	3-bromo-4-{4-[(2-chloro-4-fluorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine
49	1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-4-(4-chlorophenyl)-N-[3-(diethylamino)propyl]piperidine-4-carboxamide
50	3-bromo-4-[4-(phenylmethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine
51	2-[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-pyridin-2-ylacetamide
52	3-bromo-4-[4-(1H-imidazol-2-ylmethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine
53	3-bromo-4-(4-{[3-(phenyloxy)phenyl]methyl}piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine
54	3-bromo-4-{4-[(3-methylphenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine
55	3-{[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]methyl}benzonitrile
56	3-bromo-4-{4-[(2-chloro-6-fluorophenyl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine
57	3-bromo-4-[4-(1-phenylethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine
58	3-bromo-4-[4-(pyridin-4-ylmethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine
59	1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-N-(4-chlorophenyl)piperidin-4-amine
60	3-bromo-4-[4-(pyridin-3-ylmethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine
61	3-bromo-4-(4-{[2,3,4-tris(methyloxy)phenyl]methyl}piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine

Table 3

Entry	Name
62	3-bromo-4-[4-({3-[(phenylmethyl)oxy]phenyl}methyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine
63	3-bromo-4-[4-(naphthalen-1-ylmethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine
64	3-bromo-4-(4-{[5-(4-chlorophenyl)furan-2-yl]methyl}piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine
65	3-bromo-4-[4-({4-[(4-fluorophenyl)oxy]-3-nitrophenyl}methyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine
66	3-bromo-4-[4-(furan-2-ylcarbonyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine
67	3-bromo-4-[4-(1H-indol-6-ylcarbonyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine
68	3-bromo-4-{4-[2-(2-thienyl)ethyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine
69	3-bromo-4-[4-(3-pyrrolidin-1-ylpropyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine
70	3-bromo-4-[4-(cyclohexylmethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine
71	3-bromo-4-{4-[(10-chloroanthracen-9-yl)methyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine
72	3-bromo-4-[4-(1-methylpropyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine
73	4-(4-{[4,6-bis(methyloxy)pyrimidin-2-yl]methyl}piperazin-1-yl)-3-bromo-1H-pyrazolo[3,4-d]pyrimidine
74	3-bromo-4-{4-[2-(methyloxy)ethyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine
75	3-bromo-4-[4-(2-morpholin-4-yl-2-oxoethyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine
76	3-bromo-4-{4-[3-(methyloxy)propyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine
77	4-{4-[[4,6-bis(methyloxy)pyrimidin-2-yl](phenyl)methyl]piperazin-1-yl}-3-bromo-1H-pyrazolo[3,4-d]pyrimidine
78	3-bromo-4-[4-(6,7,8,9-tetrahydro-5H-benzocyclohepten-5-yl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine
79	3-bromo-4-[4-({4-[(phenylmethyl)oxy]phenyl}methyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine
80	3-bromo-4-[4-({3-chloro-4-[(phenylmethyl)oxy]phenyl}methyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine
81	4-{[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]methyl}-N-(3-morpholin-4-ylpropyl)benzamide
82	4-{[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]methyl}-N-[3-(methyloxy)propyl]benzamide
83	2-[({4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-1-[(4-chlorophenyl)methyl]piperazin-2-yl}methyl)oxy]-N,N-dimethylethanamine

Table 3

Entry	Name
84	3-bromo-4-[4-({4-[(4-chlorophenyl)oxy]-3-nitrophenyl}methyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine
85	2-[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N,N-dimethylacetamide
86	2-{[(R)-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]oxy}-N,N-dimethylethanamine
87	N-(4-bromo-3-fluorophenyl)-N-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-N'-[2-(dimethylamino)ethyl]urea
88	2-({(R)-(4-chlorophenyl)[1-(3-ethyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]methyl}oxy)-N,N-dimethylethanamine
89	2-{[(S)-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]oxy}-N,N-dimethylethanamine
90	3-bromo-4-(4-{(R)-(4-chlorophenyl)[(2-pyrrolidin-1-ylethyl)oxy]methyl}piperidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine
91	1-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-1-(4-chlorophenyl)-4-(dimethylamino)butan-1-ol
92	2-{[(R)-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chloro-3-fluorophenyl)methyl]oxy}-N,N-dimethylethanamine
93	3-bromo-4-(4-{(R)-(4-chlorophenyl)[(2-piperidin-1-ylethyl)oxy]methyl}piperidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine
94	4-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-4-(4-chlorophenyl)-N,N-dimethylbutan-1-amine
95	3-bromo-4-(4-{(R)-(4-chlorophenyl)[(2-morpholin-4-ylethyl)oxy]methyl}piperidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine
96	1-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-1-(4-fluorophenyl)-N-(furan-2-ylmethyl)-N-methylmethanamine
97	1-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-1-(4-fluorophenyl)-N-methyl-N-(pyridin-2-ylmethyl)methanamine
98	4-{[{[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-fluorophenyl)methyl}(methyl)amino]methyl}-N,N-dimethylaniline
99	[4-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl](1H-indol-6-yl)methanol
100	3-bromo-4-(4-{(R)-(4-chloro-3-fluorophenyl)[(2-pyrrolidin-1-ylethyl)oxy]methyl}piperidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine
101	3-bromo-4-{4-[(4-chlorophenyl)oxy]piperidin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine
102	2-{[(R)-[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]oxy}-N,N-diethylethanamine
103	2-{[1-(3-bromo-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]oxy}-5-chloro-N-(2-pyrrolidin-1-ylethyl)aniline

49. A pharmaceutical composition comprising the compound according to any one of claims 1 - 48 and a pharmaceutically acceptable carrier.

50. A metabolite of the compound or the pharmaceutical composition according to any one of claims 1 - 49.

51. A method of modulating the *in vivo* activity of a kinase, the method comprising administering to a subject an effective amount of a composition comprising at least one of: the compound according to any of claims 1- 48, the pharmaceutical composition according to claim 49, a compound explicitly provided against in claim 2, and a pharmaceutical composition comprising a compound explicitly provided against in claim 2 and a pharmaceutically acceptable carrier.

52. The method according to claim 51, wherein the kinase is p70S6K.

53. The method according to claim 52, wherein modulating the *in vivo* activity of p70S6K comprises inhibition of p70S6K.

54. A method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities, the method comprising administering, to a mammal in need thereof, a therapeutically effective amount of a composition comprising at least one of: the compound according to any of claims 1 - 48, the pharmaceutical composition according to claim 49, a compound explicitly provided against in claim 2, and a pharmaceutical composition comprising a compound explicitly provided against in claim 2 and a pharmaceutically acceptable carrier.

55. A method of screening for modulator of at least one of a p70S6, Akt-1 and Akt-2 kinase, the method comprising combining either a compound according to any one of claims 1 - 48 or a compound, the composition of which was explicitly provided against in claim 2, and at least one candidate agent and determining the effect of the candidate agent on the activity of said kinase.

56. A method of inhibiting proliferative activity in a cell, the method comprising administering an effective amount of: the compound according to any of claims 1 - 48, the pharmaceutical composition according to claim 49, a compound, the composition of which was, explicitly provided against in claim 2, and a pharmaceutical composition comprising a compound, the composition of which was, explicitly provided against in claim 2 and a pharmaceutically acceptable carrier.

57. A method of inhibiting abnormal metabolic activity in a cell, the method comprising administering an effective amount of: the compound according to any of claims 1 - 48, the pharmaceutical composition according to claim 49, a compound, the composition of which was, explicitly provided against in claim 2, and a pharmaceutical composition comprising a compound, the composition of which was, explicitly provided against in claim 2 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/046938

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/519 A61P35/00 A61P29/00 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHERN, JYH-HAUR ET AL: "Design, synthesis, and structure-activity relationships of pyrazolo[3,4-d]pyrimidines: a novel class of potent enterovirus inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS , 14(10), 2519-2525 CODEN: BMCLE8; ISSN: 0960-894X, vol. 14, no. 10, 17 May 2004 (2004-05-17), XP004841231 scheme 3, compound 9	1-47

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 May 2006	01/06/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schuemacher, A

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/046938

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MATSUNO, KENJI ET AL: "Potent and Selective Inhibitors of Platelet-Derived Growth Factor Receptor Phosphorylation. 3. Replacement of Quinazoline Moiety and Improvement of Metabolic Polymorphism of 4-[4-(N-Substituted (thio)carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazoline Derivatives" JOURNAL OF MEDICINAL CHEMISTRY , 46(23), 4910-4925 CODEN: JMCMAR; ISSN: 0022-2623, 2003, XP002362055 Table 3, compound 39b	1-51,54, 56,57
Y	WU, TOM Y. H. ET AL: "One-Pot Two-Step Microwave-Assisted Reaction in Constructing 4,5-Disubstituted Pyrazolopyrimidines" ORGANIC LETTERS , 3587-3590 CODEN: ORLEF7; ISSN: 1523-7060, vol. 5, no. 20, 2003, XP002376657 table 1, compound 21	1-51,54, 56,57
Y	QUINTELA, JOSE M. ET AL: "6-Dimethylamino 1H-Pyrazolo[3,4-d]pyrimidine derivatives as new inhibitors of inflammatory mediators in intact cells" BIOORGANIC & MEDICINAL CHEMISTRY , 11(6), 863-868 CODEN: BMECEP; ISSN: 0968-0896, 2003, XP002376658 scheme 1, compounds 7c, 8c and 9c	1-51,54, 56,57
Y	QUINTELA, JOSE M. ET AL: "Pyrazolopyrimidines: synthesis, effect on histamine release from rat peritoneal mast cells and cytotoxic activity" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY , 36(4), 321-332 CODEN: EJMCA5; ISSN: 0223-5234, 2001, XP004255694 compound 5d, figure 2	1-47
Y	US 6 423 716 B1 (MATSUNO, KENJI ET AL) 23 July 2002 (2002-07-23) Table 1-4, col. 24-25; col. 57, l.37-46;	1-51,54, 56,57
P,X	WO 2005/051304 A2 (ARRAY BIOPHARMA INC., USA) 9 June 2005 (2005-06-09) claims 1,22; figure 35; examples 100,106	1-57
P,X	WO 2005/117909 A2 (EXELIXIS, INC., USA) 15 December 2005 (2005-12-15) the whole document	1-57
P,Y	WO 2005/085249 A1 (USA) 15 September 2005 (2005-09-15) claims 1,29; examples 39,51,53,94	1-51,54, 56,57

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/046938

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 51-57 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2005/046938

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6423716 B1	23-07-2002	AU 3053999 A	25-10-1999
		CA 2326324 A1	14-10-1999
		EP 1067123 A1	10-01-2001
		WO 9951582 A1	14-10-1999
WO 2005051304 A2	09-06-2005	NONE	
WO 2005117909 A2	15-12-2005	NONE	
WO 2005085249 A1	15-09-2005	NONE	